OCTOBER 1954

BULLETIN

OF THE NEW YORK ACADEMY OF MEDICINE

Original Articles

by

I. HERBERT SCHEINBERG

SOLOMON A. BERSON

IAGO GALDSTON

THE FAILING HEART

Transcription of a Panel Meeting

CHARLES E. KOSSMANN ROBERT C. BATTERMAN

CARY EGGLESTON LUDWIG EICHNA

CHARLES K. FRIEDBERG

Through its three-fold action in arthritis... relief of pain, improvement of function, and resolution of inflammation... BUTAZOLIDIN contributes significantly to the rehabilitation of the arthritic patient.

In addition to its marked therapeutic effectiveness, the advantages of BUTAZOLIDIN include:

Wide Scope of Usefulness—effective in the most crippling and chronic arthritides.

Persistence of Effect—does not provoke tolerance on continued usage.

Nonhormonal in Character—the therapeutic action of BUTAZOLIDIN is not mediated through the pituitary-adrenocortical axis.

BUTAZOLIDIN being a potent agent, the physician should carefully select candidates for treatment and promptly adjust dosage to the minimal individual requirement. Patients should be regularly examined during treatment, and the drug discontinued should side reactions develop.

Detailed literature on request.

BUTAZOLIDIN® (brand of phenylbutazone): Red sugar-coated tablets of 100 mg.

in arthritis and allied disorders

BUTAZOLIDIN

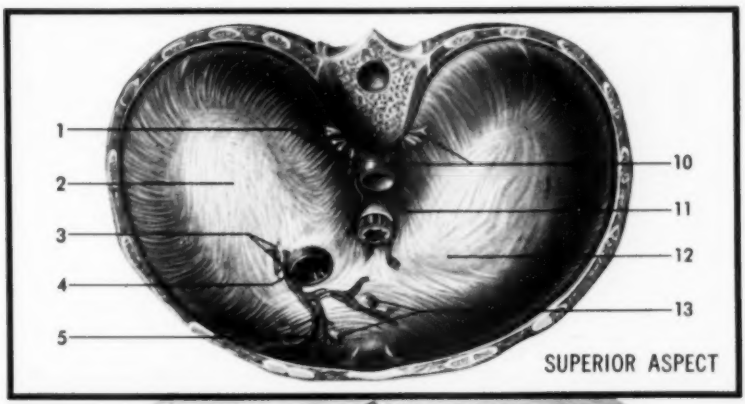
nonhormonal anti-arthritic

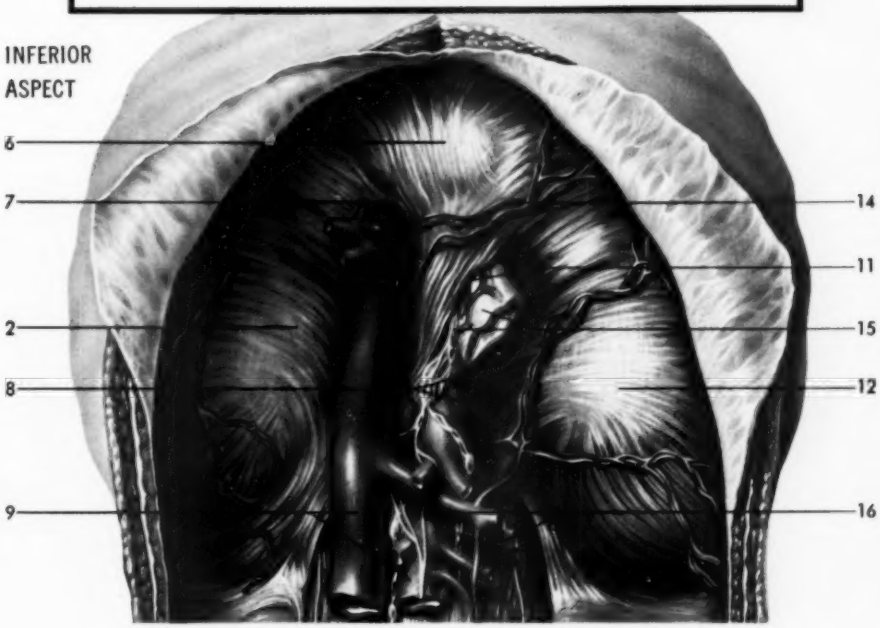
relieves pain • improves function • resolves inflammation

CIBA

CIBA PHARMACEUTICALS
Division of Ciba Chemical Corporation
220 Church Street, New York 13, N. Y.
In Canada:
Ciba Pharmaceuticals, Montreal

The Diaphragm





1 Azygos vein
2 Right leaflet
3 Phrenic nerve; pericardiacophrenic artery
4 Vena cava
5 Superior phrenic artery and vein
6 Middle leaflet
7 Vena caval foramen
8 Aortic hiatus
9 Inferior vena cava; abdominal aorta
10 Aorta; sympathetic trunk
11 Esophageal hiatus
12 Left leaflet
13 Diaphragmatic lymph nodes
14 Inferior phrenic artery and vein
15 Esophagus; vagus nerve
16 Left renal artery and vein

This is one of a series of paintings by Paul Peck, illustrating the anatomy of various organs and tissues of the body which are frequently attacked by infection, where Aureomycin may prove useful.

Lederle

Aureomycin*

HYDROCHLORIDE CHLORTETRACYCLINE HCl

in Gastrointestinal Infections

AUREOMYCIN has an established place in the treatment of infectious diarrhea, including bacillary dysentery. There are, likewise, well-documented reports to show that AUREOMYCIN is useful in the treatment of certain types of epidemic diarrhea of infancy.

AUREOMYCIN is effective for preoperative prophylaxis in patients undergoing operative procedures on the gastrointestinal tract. The danger of peritonitis is greatly decreased and the risk of delayed healing due to infection is minimized.

Available in Oral, Parenteral and Ophthalmic Dosage Forms

LEDERLE LABORATORIES DIVISION

AMERICAN Cyanamid COMPANY

Pearl River, New York

*Trade-Mark

WHICH IS THE LARGER PANEL ???

Although the panel at the right seems a good bit larger, both are actually identical in size. Your eyes may sometimes deceive you, BUT . . .

. . . ANY WAY YOU LOOK AT IT . . .

YOU'RE ALWAYS RIGHT WITH

RAWL

WHOLE LIVER

Vitamin B Complex Capsules

Provides **unfractionated whole liver,** most complete B complex source; contains essential factors missing from all other natural sources. Contains all the essential amino acids.

In all conditions characterized by deficiency of factors of the vitamin B complex — in endocrine disturbance related to impairment of liver functions, such as: premenstrual tension, diminished libido and potency in the male and diabetes.

In bottles of 100 and 500

"Restoration of healthy self-regulatory mechanisms should be the primary aim of nutritional therapy. This can only be accomplished by supplying simultaneously **all** the necessary macro- and micronutrients in sufficiently intensive but not excessive amounts and in reasonable proportion." M. S. Biskind, M. D., Amer. J. Dig. Dis. March, 1953.

Write Today for Free Samples and Literature

RAWL CHEMICAL COMPANY

Pioneers in Whole Liver Vitamin Therapy

303 FOURTH AVENUE • NEW YORK 10, N. Y.

- highly soluble in both acid and alkaline body fluids, especially at pH of renal tubules
- high plasma levels rapidly attained
- no alkalinization or forcing of fluids required
- single sulfonamide - not a mixture
- no danger of secondary fungus infections
- wide antibacterial range

you prescribe
these distinctive features
when you prescribe . . .

Hoffmann - La Roche Inc • Roche Park • Nutley 10 • N.J.

GANTRISIN® – brand of sulfisoxazole (3,4-dimethyl-5-sulfanilamido-isoxazole)

The Bulletin of The New York Academy of Medicine, Vol. 30, No. 10, October, 1954. Published Monthly by The New York Academy of Medicine, 2 East 103 Street, New York 29, N. Y. Entered as second-class matter February 3, 1928, at the Post Office at New York, N. Y., under the Act of August 24, 1912. Annual subscription United States and Canada $6.50 All other countries $7.50. Single copies, 75c.

Combination tranquilizer-antihypertensive

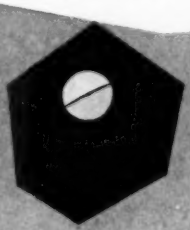
especially for moderate and severe essential hypertension . . .

T.M.

Serpasil-Apresoline®

hydrochloride

(RESERPINE AND HYDRALAZINE HYDROCHLORIDE CIBA)



Combined in a Single Tablet

- The tranquilizing, bradycrotic and mild antihypertensive effects of Serpasil, a pure crystalline alkaloid of rauwolfia root.
- The more marked antihypertensive effect of Apresoline and its capacity to increase renal plasma flow.

Each tablet (scored) contains 0.2 mg. of Serpasil and 50 mg. of Apresoline hydrochloride.

CIBA

SUMMIT, N. J.

MULL-SOY *proved*

by the test of time

medical experience with MULL-SOY for milk allergy is measured by constant general clinical use since 1934 . . . and by constant favorable reference in the literature since 1944[1-13]

1. Cahill, W. M.: Schroeder, L. J., and Smith, A. H.: J. Nutrition 28:209, 1944. 2. Stoesser, A. V.: Ann. Allergy 4:494, 1944. 3. Schroeder, L. J.: Cahill, W. M., and Smith, A. H.: J. Nutrition 32:43, 1946. 4. Stoesser, A.V.: J. Allergy 18:29, 1947. 5. Clein, N. W.: Ann. Allergy 9:195, 1951. 6. Sternberg, S. D., and Greenblatt, I. J.: Ann. Allergy 9:190, 1951. 7. Sobel, S. H.: Clin. Med. 59:362, 1952. 8. Glaser, J., and Johnstone, D. E.: Ann. Allergy 10:433, 1952. 9. Stoesser, A. V., and Nelson, L. S.: Journal-Lancet 73:487, 1953. 10. Glaser, J., and Johnstone, D. E.: J.A.M.A. 153:620, 1953. 11. Johnstone, D. E., and Glaser, J.: J. Allergy 24:434, 1953. 12. Moore, I. H.: Journal-Lancet 74:80, 1954. 13. Speer, F.: Ann. Allergy 12:168, 1954.

...and still improving

new

MULL-SOY® Powdered

HYPOALLERGENIC SOY FOOD FOR INFANTS, CHILDREN AND ADULTS

for new acceptance, new flexibility, new convenience in the management of milk allergy

Available: in 1-lb. tins at all drug outlets.

Introductory formula — 1 level tablespoon per 3 fl.oz. water.

Standard formula—1 level tablespoon per 2 fl.oz. water.

STILL AVAILABLE: time-tested MULL-SOY Liquid — easy to use as evaporated milk. In 15½-fl.oz. tins at all drug outlets.

Nutritional counterpart of time-tested MULL-SOY Liquid. Assures the utmost in acceptability for milk-allergic patients at any age level. MULL-SOY Powdered is light-colored, quickly soluble, readily digested... exceptionally easy to prepare and pleasant to take. Offers minimal likelihood of loose stools.

for clinical literature and samples write:

Borden's PRESCRIPTION PRODUCTS DIVISION
350 Madison Avenue, New York 17

WYBIOTIC*

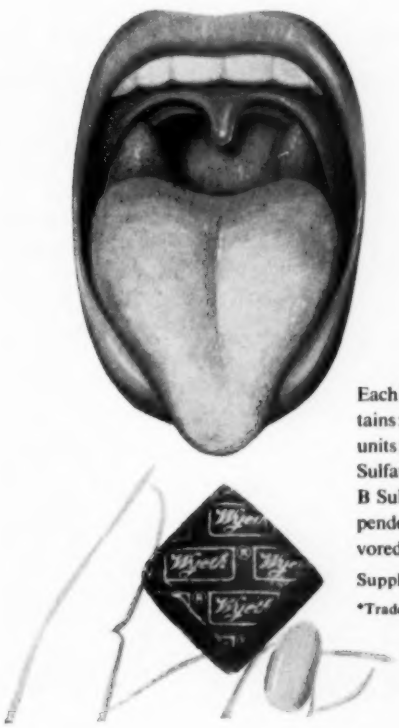
BACITRACIN • NEOMYCIN • POLYMYXIN

TROCHES

FOR SORE THROAT

Three antibiotics in potentiating action . . . WYBIOTIC Troches are formulated for wide-range bactericidal action with extraordinary freedom from sensitization and bacterial resistance. For non-febrile mouth and throat infections, both gram-negative and gram-positive. No danger of sensitizing the patient to antibiotics that may be needed systemically in later serious illness, nor of developing in him resistance to these antibiotics.

EFFECTIVE . . . . PALATABLE . . . . SAFE



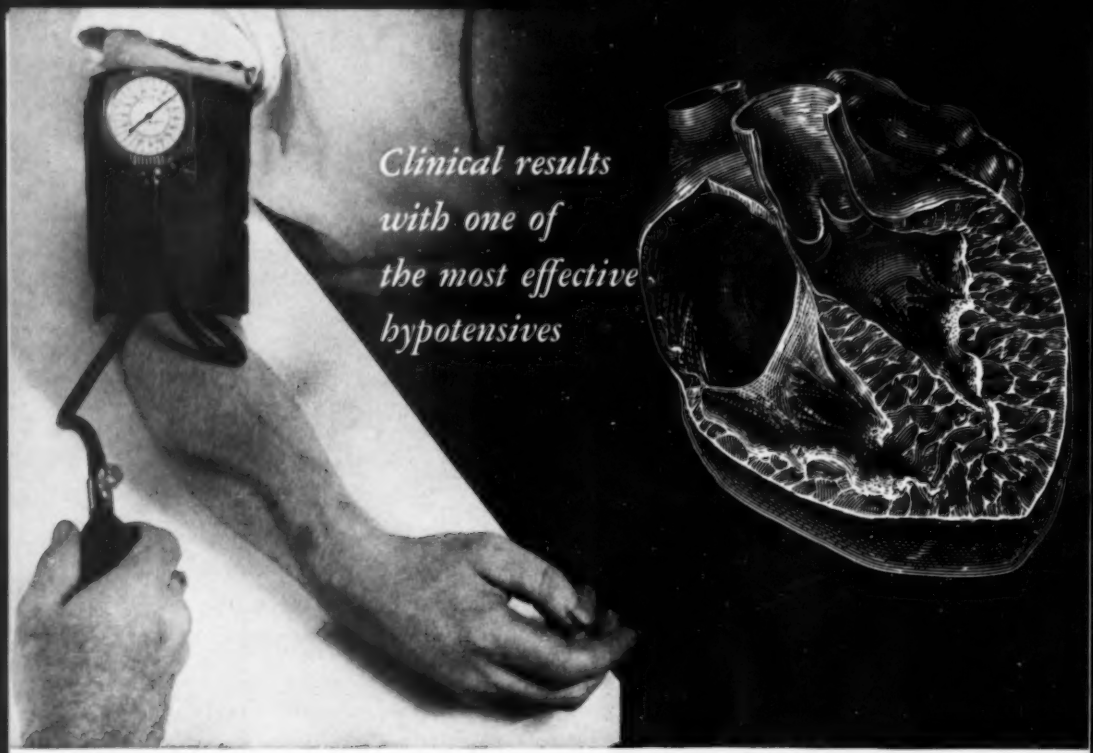
Each WYBIOTIC Troche contains: Zinc Bacitracin, 300 units; Neomycin Base (as Sulfate), 5 mg.; Polymyxin B Sulfate, 2000 units. Suspended in pleasantly flavored candy base.

Supplied: Cans of 48 troches.

*Trademark

Wyeth

Philadelphia 2, Pa.



Improvement in 67 to 72% of patients with hypertensive heart disease[1]

Together with significant reductions of elevated blood pressure in 80 per cent of outpatient hypertensives,[1] Methium therapy may result in substantial improvement in cardiac symptoms and signs.[1,2,3] Precordial pain, ventricular strain, heart failure and hypertrophy may all respond to careful treatment.[1,2,3] Actual myocardial damage, however, seldom shows any improvement (only 8 out of 44 in one study[1]).

With continued management, up to or beyond a year, blood pressure may be reduced and stabilized, and cardinal symptoms arrested or reversed, without any increase in dosage.[1]

As blood pressure is reduced, and even without reduction, hypertension symptoms have regressed. Retinopathy may disappear; headache, cardiac failure and kidney function may improve.

Methium, a potent autonomic ganglionic blocking agent, reduces blood pressure by interrupting nerve impulses responsible for vasoconstriction. Because of its potency, careful use is required. Pretreatment patient-evaluation should be thorough. Special care is needed in impaired renal function, coronary disease and existing or threatened cerebral vascular accidents.

Bibliography:

1. Moyer, J. H.; Miller, S. I., and Ford, R. C.: J.A.M.A. *152*:1121 (July 18) 1953.
2. Moyer, J. H.; Snyder, H. B.; Johnson, I.; Mills, L. C., and Miller, S. I.: Am. J. M. Sc. *225*:379 (April) 1953.
3. Kuhn, P. H.: Angiology *4*:195 (June) 1953.

Methium® CHLORIDE

(BRAND OF HEXAMETHONIUM CHLORIDE)

WARNER-CHILCOTT *Laboratories* NEW YORK

Is there an engineer in the waiting room?

You, as a physician, are thoroughly trained and experienced in detecting the clinical conditions that affect your patients' physical being. They depend on you completely for a knowledge and guidance not possessed by themselves. Conversely, do you not similarly look to professional men in other fields for aid when the need arises?

For example, when there's the question of quality in the consideration of a new piece of diagnostic equipment — such as an electrocardiograph — an engineer can tell better than anyone, sometimes with just a superficial examination, how well the instrument is designed and made. He notices such things as workmanship, the quality of materials, and the grade of the components. As an engineer he would be sure to see the value in unitized construction in the Viso-Cardiette — amplifier, control panel and recorder as three basic assemblies — and the advantages of inkless recording in true rectangular coordinates. He would remark about the minimum of moving parts, the ruggedness of construction, and the precision instrument quality of the purchased components.

If you are trying to decide which electrocardiograph to buy, we invite this type of comparison between the Viso-Cardiette and any other instrument. To make such an examination of the Viso possible, you may have a Viso for a 15-day trial* without any obligation whatsoever.

* This EXCLUSIVE plan places a Viso-Cardiette in your hands for 15 days. At the end of that trial period, if you are not completely satisfied with the instrument, you simply return it to us and that is all! You're under NO OBLIGATION.

SANBORN COMPANY

NEW YORK, *Branch Office*
1860 Broadway, Circle 7-5794-5795

a favorite

prescription

the year 'round

to **accelerate**

healing

DESITIN® ointment

the pioneer external **cod liver oil** therapy

New impressive studies[1] again confirm the clinical value[2-4] of Desitin Ointment to protect, soothe, facilitate healthy granulation, and speed healing even in stubborn skin conditions often resistant to other therapy.

in **wounds • burns • ulcers** (decubitus, varicose, diabetic)

diaper rash • intertrigo

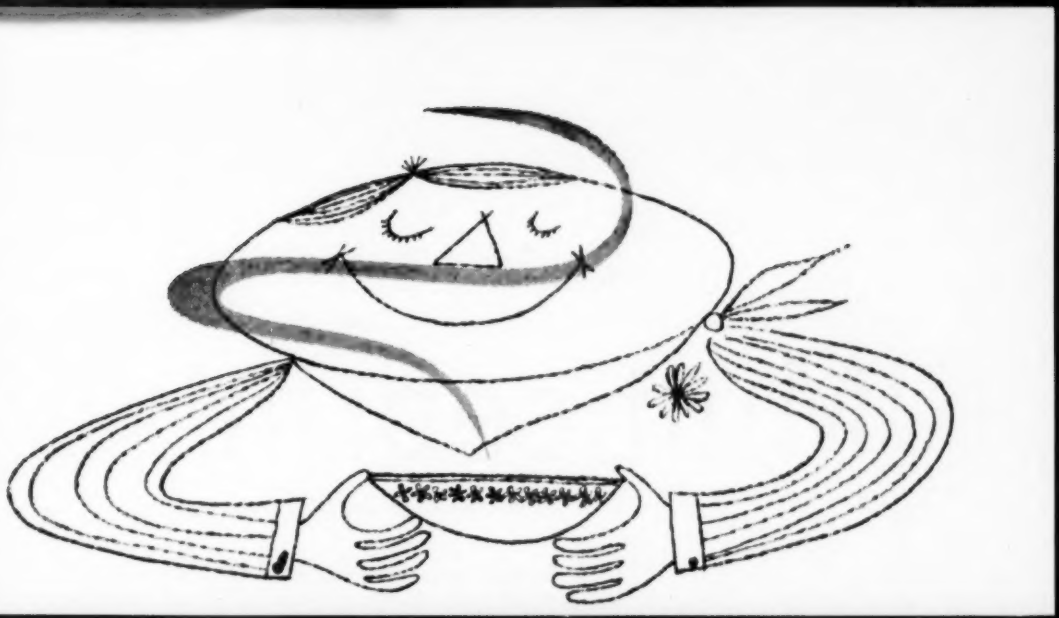
non-specific dermatoses • perianal dermatitis

Protective, soothing, healing, Desitin Ointment is a non-irritating, non-sensitizing blend of high grade Norwegian cod liver oil (with its unsaturated fatty acids and high potency vitamins A and D in proper ratio for maximum efficacy), zinc oxide, talcum, petrolatum, and lanolin. Desitin Ointment does not liquefy at body temperature and is not decomposed or washed away by secretions, exudate, urine or excrements. Dressings easily applied and painlessly removed. Tubes of 1 oz., 2 oz., 4 oz., and 1 lb. jars.

samples and reprint[1] on request

DESITIN CHEMICAL COMPANY
70 Ship Street, Providence 2, R. I.

1. Grayzel, H. G., Heimer, C. B., and Grayzel, R. W.: New York St. J. M. 53:2233, 1953.
2. Heimer, C. B., Grayzel, H. G., and Kramer, B.: Archives of Pediatrics 68:382, 1951.
3. Behrman, H. T., Combes, F. C., Bobroff, A., and Leviticus, R.: Ind. Med. & Surgery 18:512, 1949.
4. Turell, R.: New York St. J. M. 50:2282, 1950.



salt-free needn't mean flavor-free

DIASAL is enthusiastically endorsed by low salt dieters for the zest and flavor it gives to pallid, sodium restricted meals. So closely does it match the appearance, texture and taste of table salt that patient adherence to your diet instructions is virtually assured.

DIASAL contains only potassium chloride, glutamic acid and inert ingredients — no sodium, lithium, or ammonium. It may be used safely for extended periods, both at the table and in cooking. Because of its potassium, DIASAL may be a valuable prophylactic against potassium depletion.

DIASAL®

packaging: available in 2-ounce shakers and 8-ounce bottles.
Send for liberal supplies of tasting samples and low sodium diet sheets for your patients.

FOUGERA

E. FOUGERA & COMPANY, INC.
75 Varick Street, New York 13, N. Y.

Prevent vitamin deficiency

'Multicebrin'

(Pan-Vitamins, Lilly)

when in doubt about dietary vitamin intake, prescribe 'Multicebrin'—a complete, carefully standardized multiple-vitamin product.

Each gelseal provides:		
Thiamin Chloride	3	mg.
Riboflavin	3	mg.
Pyridoxine Hydrochloride	1.5	mg.
Pantothenic Acid (as Calcium Pantothenate)	5	mg.
Nicotinamide	25	mg.
Vitamin B_{12} (Activity Equivalent)	3	mcg.
Folic Acid	0.1	mg.
Ascorbic Acid	75	mg.
Distilled Tocopherols, Natural Type	10	mg.
Vitamin A Synthetic	10,000	U.S.P. units
Vitamin D Synthetic	1,000	U.S.P. units

IN BOTTLES OF 100 AND 1,000 GELSEALS.

Lilly

QUALITY / RESEARCH / INTEGRITY

ELI LILLY AND COMPANY, INDIANAPOLIS 6, INDIANA, U.S.A.

SECOND SERIES OCTOBER 1954 VOL. 29, NO. 10

BULLETIN OF THE NEW YORK ACADEMY OF MEDICINE

CONTENTS

Clinical Implications of Plasma Fractionation . . . 735
I. Herbert Scheinberg

Blood Volume in Health and Disease 750
Solomon A. Berson

The Failing Heart

Transcription of a Panel Meeting on Therapeutics 777
Charles E. Kossmann, Robert C. Batterman, Cary Eggleston, Ludwig Eichna and Charles K. Friedberg

Sophocles contra Freud: A Reassessment of the Oedipus Complex 803
Iago Galdston

AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

ROBERT L. CRAIG, *Editor*

Published Monthly by THE NEW YORK ACADEMY OF MEDICINE
2 East 103 Street, New York 29, N. Y.

ADVERTISING OFFICE • 30 ROCKEFELLER PLAZA, N. Y. C. 20 • CIRCLE 7-7706

Copyright, 1954 by The New York Academy of Medicine

OFFICERS AND STAFF OF THE ACADEMY

1954

President

ALEXANDER T. MARTIN

Vice-Presidents

EDWARD J. DONOVAN — CLAUDE E. FORKNER — JEROME P. WEBSTER

Treasurer

SHEPARD KRECH

Recording Secretary

FREDERICK H. WILKE

Trustees

GEORGE BAEHR — *SHEPARD KRECH — HENRY ALSOP RILEY
ARTHUR F. CHACE — ASA L. LINCOLN — BENJAMIN P. WATSON
BRADLEY L. COLEY — *ALEXANDER T. MARTIN — ORRIN S. WIGHTMAN
CONDICT W. CUTLER, JR. — HAROLD R. MIXSELL — *FREDERICK H. WILKE
WILLIAM BARCLAY PARSONS

Council

The President — The Vice-Presidents — The Trustees
The Treasurer — The Recording Secretary
The Chairmen of Standing Committees

Director

HOWARD REID CRAIG

Librarian

JANET DOE

Executive Secretary
Public Health Relations Committee

HARRY D. KRUSE

Executive Secretary
Committee on Medical Education

ROBERT L. CRAIG

Executive Secretary
Committee on Medical Information

IAGO GALDSTON

Comptroller

ARTHUR A. EBERLE

Legal Counsel

JOHN W. DAVIS, ESQ.

Library Consultants

B. W. WEINBERGER, CURT PROSKAUER

EDITORIAL BOARD

JEROME P. WEBSTER, *Chairman*
DAVID P. BARR
MARGARET BEVANS
WILLIAM DOCK
JANET DOE
JOHN G. KIDD
ROBERT F. LOEB
LOUIS M. ROUSSELOT

ROBERT L. CRAIG, *Secretary and Editor*

* Ex-officio

BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

VOL. 30, NO. 10 OCTOBER 1954

CLINICAL IMPLICATIONS OF PLASMA FRACTIONATION*

I. HERBERT SCHEINBERG

Principal Research Scientist (Internal Medicine), New York State Psychiatric Institute; Assistant Professor of Medicine, College of Physicians & Surgeons, Columbia University, New York, N. Y.

MANY of the functions of blood are performed by plasma. The fundamental postulate which underlies plasma fractionation is that many functions of plasma are due to the properties of specific plasma components. There are many types of plasma components including such diverse classes of substances as minerals, carbohydrates, and fats. This paper, however, will be limited to a discussion of the consequences of separating the proteins of plasma into preparations which, so far as possible, consist of a single protein.

A detailed consideration of the methods by which plasma fractionation is carried out will not be undertaken, but some reference to the principles involved will be helpful. The most successful plasma fractionation procedure yet devised, and the one which has provided all the commonly used human plasma fractions now available to physicians, is the five-variable system developed by the late Professor Edwin J. Cohn, and his colleagues,[1,2] at Harvard.† This method rests on the assumption

* Presented at the 26th Graduate Fortnight of The New York Academy of Medicine, October 30, 1953.
† The plasma which was used in these studies came from blood collected by the American Red Cross.

that each protein, being a unique component, will under proper conditions, have a different solubility from every other protein. Therefore, each protein could eventually be selectively precipitated and separated from a solution which still contained several other proteins. The variables which define the conditions under which the fractionations occur are the temperature, and the concentrations of ethyl alcohol, of proteins, of hydrogen ions, and of all other small ions such as sodium and chloride.* The description of these protein fractions by numbers, such as I, II and V, refers to the order in which they are precipitated from plasma.

In the past several years Professor Cohn and his associates have been engaged in developing a new method of fractionation.[3-6] This was designed to concentrate and purify plasma proteins in their "state in nature." For this purpose several fundamental modifications of the five-variable system have been introduced. The use of sodium citrate as an anticoagulant when blood is drawn is replaced by an ion exchange resin which removes plasma calcium. The solubilities of the different protein fractions are varied by taking advantage of specific interactions of proteins with metals, such as zinc ions. Consequently, the addition of alcohol and acid buffers, essential parts of the old method, is eliminated. Further, the proteins are fractionally extracted from the relatively stable solid state instead of being fractionally precipitated from solution. This replacement of the sodium citrate, ethyl alcohol and low pH of the old method, which had clearly denatured some proteins and had presumably destroyed others of which little was yet known, by the new reagents and procedures is less likely to alter the characteristics of native proteins.

Table I lists some of the plasma proteins and their physiologic functions. When one considers that the gamma globulins can include innumerable specific antibodies, each of which is a unique protein,[7] that several proteins which play a role in coagulation have been recently discovered, [8, 9] and that there are proteins, like the acid glycoprotein,[10] concerning which little physiologic information is available,[11, 12] it is clear that the eventual number of plasma proteins with which clinicians will be concerned may be closer to a hundred than to the venerable pair which defines the albumin-globulin ratio.

There are at least five advantages to fractionating plasma. Chemical, physiologic and clinical information is obtained; therapy with plasma

* Strictly, the last two variables are not the concentrations of hydrogen ions and small ions but the pH and ionic strength, respectively, which are closely related to concentrations.

TABLE I—PLASMA PROTEINS

Function	*Components*
Oncotic Pressure	Albumins α-, β-, Globulins
Coagulation	Prothrombin Ac-Globulin Antihemophilic Globulins SPCA Precursor Fibrinogen Plasminogen
Immunity	γ-Globulins Complement
Transport	α-, β-, Lipoproteins Transferrin Albumin
Regulation	Hormones
Enzymes	Ceruloplasmin Phosphatases Esterases, etc.

is made more effective by use of plasma derivatives; blood is economically used; the stability of the products obtained is often greater than that of plasma; and greater safety is attained. A few examples will make the advantages clearer.

When a protein is prepared in a relatively pure form by fractionation, the fractionation method itself can be made more effective. This is because the conditions under which the pure protein remains soluble, or is precipitated, may be carefully defined, and its interactions with other compounds may be precisely studied. For example, the fact that the isohemagglutinins of plasma interact specifically with red cell stroma antigens made it possible to devise a method of isolating the isohemagglutinins in solution free of other antibodies.[13]

Equally important is the physiologic knowledge which the chemistry of the protein provides. An example is the insight into iron metabolism gained by an understanding of the interactions of the iron-binding protein of plasma, transferrin, with iron.[14] Conversely, clinical knowledge may stimulate chemical advances. The knowledge of the absence of a coagulation component in hemophilia led to a partly successful search for the specific protein which hemophiliacs lack.[15, 16]

The increased effectiveness of therapy with a plasma derivative is

TABLE II—COMPARISON OF PLASMA PROTEIN FRACTIONS WITH WHOLE PLASMA

Derivative	*Dating Period*	*Clinical Use*	*Max. No. Pts. Treated*	
		20 Blood Donations		
Dried Whole Plasma	5 years	Shock Hypoproteinemia	10	
		Fractionation		
Fraction I	1 yr. +	Afibrinogenemia Postpartum Hemorrhage Hemophilia	11	107
Gamma Globulin	5 yrs. +	Agammaglobulinemia Prophylaxis of infections	90	
Albumin	5 yrs.	Shock Hypoproteinemia	6	

Plus other fractions for research.

emphasized in the case of a plasma protein normally present at a low concentration but yet deficient in a patient. Whole blood or plasma may never be able to supply a sufficient quantity of the protein to overcome the deficiency without seriously overloading the circulation. An example we shall discuss in more detail is the case of fibrinogen in patients with deficiency of this protein.

The economy of blood resulting from fractionation and the stability of the products obtained are exemplified in Table II which has been modified from a table of Janeway's.[17] More than 100 patients can benefit when 5 liters of plasma are fractionated instead of the ten patients who can be treated by this amount of whole plasma. In addition, other products are obtained. Stability of fractionated proteins is at least as great as dried plasma and for some proteins, such as the coagulation components, greater. The conditions for stability are not the same for each plasma protein, and fractionation permits individualization of conditions of storage.

Perhaps the greatest disadvantage to the use of whole plasma, instead of fractions, lies in the ability of pooled plasma to transmit serum hepatitis. Neither attempts to exclude infected donors, irradiation of plasma, nor prophylactic administration of gamma globulin to recipients of plasma have proven fully effective in preventing this disease.[18-22] Fractionation,

however, provides some products, of which albumin and gamma globulin are the most important, which have probably never transmitted the disease in sharp contrast to plasma.[23-26] Newer methods of processing Fraction I, which has transmitted serum hepatitis,[17] seem to have sharply reduced, if not eliminated, the danger of serum hepatitis in patients receiving this product.[27] Thrombin from Fraction III,[28] and proteins from Fraction IV[29] have also transmitted serum hepatitis.

Clinical Use of Plasma Fractions

At present the three principal products of fractionation available to the practitioner for therapeutic use are Fraction I, Fraction II, or gamma globulin, and albumin. None of these products has as yet been prepared in appreciable quantities by the new method of plasma fractionation. In the following discussion we shall deal chiefly with the indications for Fraction I and the gamma globulins, since newly reported clinical entities have enhanced their therapeutic range.

Fraction I, the principal constituent of which is fibrinogen, is supplied as a dry powder. It is generally dissolved in 5 per cent dextrose solution and administered intravenously. There are several therapeutic indications for Fraction I.

Congenital afibrinogenemia is a hemorrhagic disease which is the manifestation of a deficiency of a single plasma protein, fibrinogen.[30] Studies have shown that the defect in these patients is probably an inability to synthesize fibrinogen rather than an increased degradation of the protein.[31] Patients have a clotting time of infinity, that is, no clot forms, and immuno-chemical studies have shown that they possess only about one three-hundredth of the normal amount of fibrinogen. Patients can bleed to death, frequently from umbilical hemorrhage in the early days of life.[30] The administration of one to two grams of Fraction I results in a rise in fibrinogen level, and a fall in clotting time, to normal ranges. This is a rare disease, but its existence and the fact that regular treatment with fibrinogen appears to keep patients perfectly well, have broad implications. There are other congenital diseases which are associated with a specific deficiency of a plasma protein, and, presumably, any one of the plasma proteins could be congenitally absent with clinical consequences dependent on the function of that protein.

Acquired afibrinogenemia can occur as the result of massive transfusions of banked blood since fibrinogen is often destroyed in conven-

tional methods of blood collection and preservation. A very interesting group of obstetrical patients with absent fibrinogen has recently been reported in detail.[32-34] In these women afibrinogenemia can apparently be a consequence of any of three conditions: 1) amniotic fluid infusion, or embolism, in a woman undergoing tumultuous labor; 2) severe premature separation of the placenta; or 3) long-standing intrauterine fetal death. In all three groups intravascular defibrination seems to occur, probably as the result of the introduction of a coagulant from the amniotic fluid or uterine contents into the maternal blood. The syndrome is associated with inability of the maternal blood to form any clot or, if a clot forms, it is at best an unstable one. Severe hemorrhage can occur into the skin and from the gastrointestinal tract as well as from the uterus. There may be some reduction in levels of prothrombin and a fibrinolysin may be demonstrable, but administration of adequate fibrinogen as Fraction I, not as blood transfusions, and appropriate obstetrical care have been successful therapeutically. The amount of fibrinogen that has been used ranged from 2½ to 12 grams with an average dose of about 4 grams.

Fraction I also contains the antihemophilic globulin, a specific plasma protein essential for normal coagulation, which hemophiliacs presumably lack congenitally.[15, 16] Hemophilia is another example of the group of diseases characterized by congenital deficiency of a specific plasma protein. Two to six hundred milligrams of Fraction I, given intravenously, can markedly shorten the clotting time of a hemophiliac patient's blood. Unfortunately, preparations of Fraction I suitable for use in hemophilia must be made from fresh plasma, and, at present, such Fraction I is available only from the Division of Laboratories of the Michigan Department of Health. Fraction I suitable for use in afibrinogenemia is also being prepared by the Michigan laboratories on an experimental basis for the American Red Cross, with limited national distribution.[27]

Fraction II, the gamma globulin of plasma, should be termed gamma globulins since it includes many different antibodies, each of which is a specific protein. It is supplied as a 16.5 per cent solution, and unlike Fraction I and albumin, is always administered intramuscularly, from which site its absorption is prompt. Several indications for its use are known.

Congenital agammaglobulinemia is the third example of the group of diseases of which congenital afibrinogenemia and hemophilia have been

TABLE III—HISTORY OF INFECTIONS IN A BOY WITH AGAMMAGLOBULINEMIA

Age	1	2	3	4	5	6	7	8	9	10	11
Pyoderma	x	x		x			x				
Conjunctivitis		x		x							
Otitis Media		x					x				
Meningitis			x								
Sinusitis		x		x			x x		x		
Pneumonia			xx	x							
Arthritis			x			xx	x x	x			
Sepsis	x										
Viral Diseases			x V	x Mu			x H				
Organism	S	S F	F SF	S P F			F F S S	P			
Blood Culture			F	F							
Prophylactic Treatment		NONE →						T'mycin A'mycin		γ-Glob. →	

V = Varicella Mu = Mumps H = Herpes S = Staph. Aur. F = H. Inf. P = Pneum.

mentioned. Patients with this disease have a history of recurrent bacterial infection beginning in infancy, evidence of deficient antibody production and extremely low levels of serum gamma globulins despite essentially normal total proteins.[35-37] The disease may be sex-linked in its inheritance since only males have been observed to be affected congenitally,[37] although the condition may be acquired by children or adults of either sex. Table III, which was prepared by Dr. Leonard Apt of the Children's Medical Center, Boston, Massachusetts, summarizes the course of a boy with agammaglobulinemia. The effect of chemotherapy and of the administration of 0.1 gram of gamma globulin per kilogram of body weight every month, intramuscularly, is shown. Two years have now elapsed since gamma globulin prophylaxis was begun and he has had no infections in that period.

For the prophylaxis and attenuation of infections gamma globulin has found its greatest uses in three virus diseases: measles, infectious hepatitis, and poliomyelitis.[38]

The purpose of using gamma globulin in a healthy child exposed

to measles should be to produce mild measles which will permit permanent active immunity to develop. About 0.02 cc. of gamma globulin solution per pound of body weight will do this if it is given within five days of exposure. Post-measles complications are reduced tenfold by this dose.[24] When complete protection is needed 0.1 cc. per pound given within five days of exposure is effective.[25]

The value of gamma globulin in preventing infectious hepatitis (viral hepatitis A), although not serum hepatitis (viral hepatitis B), has been well shown and recently summarized.[38] Stokes and his collaborators[39] report that as little as 0.01 cc. of gamma globulin solution per pound of body weight may be a protective dose in an institutional outbreak. They suggest that during an epidemic active immunity may develop in susceptible persons given gamma globulin as a consequence of infection occurring while the passive protection conferred by the administered gamma globulin is waning. Another study, in which outbreaks of infectious hepatitis in families were reported, showed, first, that a large percentage of exposed children in a family contracted the disease; second, that gamma globulin is extremely effective in preventing the disease; and third, that adults involved in the outbreaks appear to have a relatively high degree of immunity.[40] It is still uncertain whether the aim in using gamma globulin prophylactically in this disease should be prevention of hepatitis, or attenuation so that active immunity may develop. It is also unsettled whether, despite their high degree of immunity, exposed adults should be given gamma globulin because of the potential danger of the disease in an adult.[40]

The effectiveness of gamma globulin in preventing poliomyelitis in exposed susceptible subjects has been reported by Hammon and his colleagues.[41, 42] Although their conclusions are still not final, gamma globulin appears to confer significant protection against poliomyelitis.

Gamma globulin processed from plasma pooled from the general population, which is the product discussed above, is not effective in the prophylaxis of mumps. When mumps convalescent plasma was used in the preparation of gamma globulin, however, the incidence of mumps orchitis was reduced from 27.4 per cent to 7.8 per cent in adult men given 20 cc. of gamma globulin solution intramuscularly in the first twenty-four hours of the disease.[43]

The available data with respect to the effectiveness of gamma globulin in preventing rubella are too sparse to permit definite conclusions.

Cohn[44] proposed using pooled gamma globulin, drawn from various populations at various times in dry powder form to supply a permanent record, characterizing the immunity of those populations. The information that such gamma globulin records could supply would be of great value in epidemiological investigations. If such material were available, for example, from 1918 to 1919, much light might be shed on the influenza pandemic of those years.

The third plasma fraction generally available for clinical use is albumin, or Fraction V. It is the oldest of the plasma fractions and the need for it in the treatment of wound shock was the chief reason plasma fractionation was undertaken during World War II. It has also been used to replenish protein in hypoproteinemic states and is particularly useful in those which are acute. Its use as a diuretic in such conditions as nephrosis and cirrhosis is wasteful and appears to have no beneficial effect on the underlying disease. Albumin is supplied as a 25 per cent solution and can be prepared in salt-poor solutions containing about a seventh as much sodium as osmotically equivalent plasma.[17] It is administered intravenously and has the great advantage over plasma of safety from the standpoint of homologous serum hepatitis. In the new method of protein fractionation albumin is replaced by "Stable Plasma Protein Solution" which contains all the albumin of plasma plus transferrin, glycoproteins and α-lipoproteins.[5]

I shall not consider the use of albumin in the therapy of shock but re-emphasis of a comment by Janeway concerning albumin as compared to plasma substitutes and extenders seems in order.[17] Although several extenders seem able to substitute for the osmotic activity of albumin, the latter has a fine structure which is responsible for specific binding of many different substances: metals, anions, fatty acids, drugs and organic molecules. The physiologic significance of these interactions is just being comprehended and the use of substitutes which do not possess albumin's unique fine structure and specific properties is an uncertain procedure.

Other Plasma Proteins

I should like now to turn briefly to a consideration of several plasma proteins not available for therapeutic use. The isolation and chemical investigation of these proteins have afforded insight into physiologic and pathologic mechanisms.

Transferrin is the iron-binding protein of plasma,[45, 46] and is present in plasma at a concentration of about 250 mgm. per cent.[14] It has already been discussed at the Fortnight, particularly by Dr. Granick, but it is worth while to mention again the marked specificity of this protein, which can reversibly bind iron and transport it,[14] and, at the same time, abolish the toxic properties which intravascular iron shows when uncombined to this protein.[47] Unlike fibrinogen and gamma globulin no congenital absence or deficiency of this protein has yet been reported. It would be of interest to speculate on what the clinical consequences of "atransferrinemia" might be in the light of chemical knowledge of this protein.

Ceruloplasmin, a plasma protein which contains 0.34 per cent copper, is normally present at a concentration of about 25 mgm. per cent.[48, 49] The bond between the metal and the protein moiety is an irreversible one, unlike that between iron and transferrin.[50] Almost all of the plasma copper is accounted for by ceruloplasmin,[48] which has a deep blue color much more intense than the color of an equal amount of inorganic cupric ion. Ceruloplasmin, which was elegantly crystallized, and characterized by Holmberg and Laurell,[50] is an enzyme which catalyzes the oxidation of amines, phenols and ascorbic acid. A specific deficiency, but not absence, of this protein has been found in patients with Wilson's disease.[49] This is an hereditary, progressive and fatal condition characterized by cirrhosis of the liver, degeneration of the basal ganglia and abnormalities in copper and amino acid metabolism.[51] Patients with this disease possess from 5 to 50 per cent of the normal amount of ceruloplasmin. The concentration of plasma ceruloplasmin has been measured by spectrophotometric and immunochemical methods.[49, 52] Unaffected siblings have normal levels of ceruloplasmin. The level of ceruloplasmin appears to be as low early in the course of Wilson's disease as late, and neither Laennec's cirrhosis[49] nor several other neurologic diseases are associated with deficiency of ceruloplasmin.[53]

It is possible, although not proven, that a deficiency of ceruloplasmin represents the basic defect of Wilson's disease, in analogy with agammaglobulinemia, congenital afibrinogenemia and hemophilia. These would then form a group of four diseases associated with specific deficiences of single plasma proteins. At least four other similar conditions have been described and were mentioned by Dr. Brinkhous: congential hypoprothrombinemia,[54] parahemophilia, or Ac-globulin deficiency,[55, 56] con-

genital deficiency of serum prothrombin conversion accelerator,[57] and Christmas disease or hemophilia B.[58]

It is of interest to consider the possible mechanisms of such deficiencies. Isotopic studies have clearly shown that all the plasma proteins which have been investigated are in the dynamic state, being continually synthesized and destroyed.[59] Decreased synthesis, or increased degradation, or both, could result in deficiency of a plasma protein. As mentioned above, studies on patients with congenital afibrinogenemia suggest that the basic defect is deficient synthesis,[31] and the same appears to be true for agammaglobulinemia.[37] Whether this is the mechanism in all the specific, congenital deficiencies of plasma proteins is still unknown.

Any discussion of deficiency of plasma proteins must take into account the fact that plasma proteins are not confined to the vascular compartment. A dynamic equilibrium exists between intravascular and extravascular plasma proteins.[60, 61] The amount of plasma protein present outside of the vascular compartment is about equal to the quantity in the circulation.[61] This is not only of theoretical importance but of practical significance when administering a plasma protein with the aim of raising its plasma level to a given point. Approximately twice as much protein will be needed as would be calculated from the assumption that the protein will only be distributed in the circulating plasma volume.

A final correlation of disease with plasma protein abnormalities should be mentioned. Patients with atherosclerosis exhibit a changed pattern of plasma lipoproteins. These changes have been elucidated by fractionation in the ultracentrifuge as well as by the chemical methods discussed above.[62-64] The plasma lipids, which include cholesterol, phospholipids and neutral fats, are held in solution in plasma by being bound to two different classes of proteins, the alpha and beta lipoproteins.[65, 66] That these two classes of lipoproteins are quite different compounds is indicated by the fact that the alpha lipoproteins have molecular weights of around 200,000, and a ratio of bound cholesterol to bound phospholipid of about 0.5, while these figures are, respectively, 1,300,000 and about 1.0 for the beta lipoproteins.[63, 65] Table IV, from data of Eder, Russ and Barr, shows how the partition of the total plasma cholesterol between the two classes of lipoproteins differs in subjects with atherosclerosis from the distribution in normal subjects.[67] Cholesterol determinations were done by the Sperry-Schoenheimer method.[68] Patients

TABLE IV—PARTITION OF PLASMA CHOLESTEROL BETWEEN LIPOPROTEINS IN ATHEROSCLEROSIS AND RELATED CONDITIONS

	Total plasma cholesterol	*% in Alpha*	*% in Beta*
Young normal subjects	164	26	74
Atherosclerosis	257	12	88
Nephrosis	503	4	96
Familial hypercholesterolemia	379	9	91

with nephrosis and hypercholesterolemia, conditions in which atherosclerosis is frequently found, show distributions similar to that in atherosclerosis. It is still uncertain whether these changes represent differences from normal in the amounts of the two proteins, in their functional capacity to combine with lipids or to a defect in lipid metabolism which these changes reflect. The description of these variations in lipoproteins in these diseases constitutes an important advance toward understanding the nature of atherosclerosis.

An attempt has been made in this paper to show that plasma fractionation is bound closely to clinical medicine. Fractionation has made therapeutic protein preparations available which possess a considerable number of advantages over the parent plasma from which they are derived. There is every likelihood that the number of these preparations will increase as research proceeds. Plasma fractionation has also afforded insight into physiology and disease on a chemical level by unravelling many of the functions of plasma and ascribing some of these to purified, often single, proteins. As a result, therapy with blood has become more rational, relations between single plasma proteins and disease have appeared, and several diseases have been described which indicate that congenital deficiencies of single plasma proteins may be responsible for a considerable number of hereditary illnesses.

Acknowledgment: It is a pleasure to express my appreciation to Dr. Charles A. Janeway for his help in the preparation of this paper.

REFERENCES

1. Cohn, E. J., Strong, L. E., Hughes, W. L., Jr., Mulford, D. J., Ashworth, J. N., Melin, M. and Taylor, H. L. Preparation and properties of serum and plasma proteins; a system for the separation into fractions of the protein and lipo-

protein components of biological tissues and fluids, *J. Amer. chem. Soc. 68*:459-75, 1946.

2. Strong, L. E. Blood fractionation, in *Encyclopedia of chemical technology*, edited by R. E. Kirk and D. F. Othmer, New York, Interscience Encyclopedia, Inc., 1948, v. *2*, pp. 557-83.
3. Cohn, E. J. Characterization and separation of proteins by virtue of their interactions, in *Blood cells and plasma proteins; their state in nature*, edited by James L. Tullis, New York, Academic Press Inc., 1953, pp. 18-58.
4. Cohn, E. J. Blood collection and preservation, *Proc. Amer. Assoc. Blood Banks 4*:34-37, 1951.
5. Surgenor, D. M. Recent advances in the preparation of stable plasma derivatives, *Quart. Rev. Med. 9*:145-52, 1952. (In *Int. Rec. Med. 165*, August 1952).
6. Tullis, J. L. Newer technics for the separation and fractionation of whole blood, *N. Y. St. J. Med. 53*:525-27, 1953.
7. Enders, J. F. The concentrations of certain antibodies in globulin fractions derived from human blood plasma, *J. clin. Invest. 23*:510-30, 1944.
8. Ware, A. G. and Seegers, W. H. Plasma accelerator globulin; partial purification, quantitative determination, and properties, *J. biol. Chem. 172*:699-705, 1948.
9. Alexander, B., Goldstein, R. and Landwehr, G. Prothrombin conversion accelerator of serum (SPCA); its partial purification and its properties compared with serum Ac-globulin, *J. clin. Invest. 29*:881-95, 1950.
10. Schmid, K. Preparation and properties of serum and plasma proteins; separation from human plasma of polysaccharides, peptides and proteins of low molecular weight; crystallization of an acid glycoprotein, *J. Amer. chem. Soc. 75*:60-68, 1953.
11. Howe, C. The influenza virus receptor and blood group antigens of human erythrocyte stroma, *J. Immunol. 66*:9-35, 1951.
12. Highberger, J. H., Gross, J. and Schmitt, F. O. Interaction of mucoprotein with soluble collagen; an electron microscope study, *Proc. nat. Acad. Sci. 37*:286-91, 1951.
13. Isliker, H. C. Purification of antibodies by means of antigens linked to ion exchange resins, *Ann. N. Y. Acad. Sci. 57*:225-38, 1953.
14. Laurell, C.-B. What is the function of transferrin in plasma? *Blood 6*:183-87, 1951.
15. Taylor, F. H. L., Davidson, C. S., Tagnon, H. J., Adams, M. A., Macdonald, A. H. and Minot, G. R. Studies in blood coagulation; the coagulation properties of certain globulin fractions of normal human serum in vitro, *J. clin. Invest. 24*:698-703, 1945.
16. Minot, G. R., Davidson, C. S., Lewis, J. H., Tagnon, H. J. and Taylor, F. H. L. The coagulation defect in hemophilia; the effect in hemophilia of the parenteral administration of a fraction of the plasma globulins rich in fibrinogen, *J. clin. Invest. 24*:704-07, 1945.
17. Janeway, C. A. Clinical use of blood derivatives, *J. Amer. med. Assoc. 138*: 859-65, 1948.
18. Rosenthal, N., Bassen, F. A. and Michael, S. R. Probable transmission of viral hepatitis by ultraviolet-irradiated plasma, *J. Amer. med. Assoc. 144*: 224-26, 1950.
19. Barnett, R. N., Fox, R. A. and Snavely, J. G. Hepatitis following the use of irradiated human plasma, *J. Amer. med. Assoc. 144*:226-28, 1950.
20. James, G., Korns, R. F. and Wright, A. W. Homologous serum jaundice associated with use of irradiated plasma, *J. Amer. med. Assoc. 144*:228-29, 1950.
21. Duncan, G. G., Christian, H. A., Stokes, J., Jr., Rexer, W. F., Nicholson, J. T. and Edgar, A. Evaluation of immune serum globulin as a prophylactic agent against homologous serum hepatitis, *Amer. J. med. Sci. 213*:53-57, 1947.
22. Stokes, J., Jr., Blanchard, M., Neefe, J. R., Gellis, S. S. and Wade, G. R. Methods of protection against homologous serum hepatitis; studies on the protective value of gamma globulin in homologous serum hepatitis SH virus, *J. Amer. med. Assoc. 138*:336-41, 1948.
23. Paine, R. S. and Janeway, C. A. Human

albumin infusions and homologous serum jaundice, *J. Amer. med. Assoc. 150*:199-202, 1952.

24. Janeway, C. A. Use of concentrated human serum gamma globulin in prevention and attenuation of measles, *Bull. N. Y. Acad. Med. 21*:202-22, 1945.
25. Ordman, C. W., Jennings, C. G., Jr. and Janeway, C. A. The use of concentrated normal human serum gamma globulin (human immune serum globulin) in the prevention and attenuation of measles, *J. clin. Invest. 23*:541-49, 1944.
26. Greenstein, N. M., Barenberg, L. H. and Steinberg, D. Relation of homologous serum hepatitis to prophylactic injection of human blood fractions; study of 13,755 cases with injections, *Amer. J. Dis. Child. 81*:218-25, 1951.
27. Surgenor, D. M. Personal communication to the author.
28. Porter, J. E., Shapiro, M., Maltby, G. L., Drake, M. E., Barondess, J. A., Bashe, W. J., Jr., Stokes, J., Jr., Oliphant, J. W., Diefenbach, W. C. L., Murray, R. and Leone, N. C. Human thrombin as a vehicle of infection in homologous serum hepatitis, *J. Amer. med. Assoc. 153*:17-19, 1953.
29. Hsia, D. Y., Kennell, J. H. and Gellis, S. S. Homologous serum-hepatitis following the use of Fraction IV prepared from postpartum plasma, *Amer. J. med. Sci. 226*:261-64, 1953.
30. Henderson, J. L., Donaldson, G. M. M. and Scarborough, H. Congenital afibrinogenaemia; report of a case with review of the literature, *Quart. J. Med. 14*:101-11, 1945.
31. Gitlin, D. and Borges, W. H. Studies on the metabolism of fibrinogen in two patients with congenital afibrinogenemia, *Blood 8*:679-86, 1953.
32. Reid, D. E., Weiner, A. E. and Roby, C. C. Intravascular clotting and afibrinogenemia; the presumptive lethal factors in the syndrome of amniotic fluid embolism, *Amer. J. Obstet. Gynec. 66*: 465-74, 1953.
33. Weiner, A. E., Reid, D. E. and Roby, C. C. Incoagulable blood in severe premature separation of the placenta; a method of management, *Amer. J. Obstet. Gynec. 66*:475-99, 1953.
34. Reid, D. E., Weiner, A. E., Roby, C. C. and Diamond, L. K. Maternal afibrinogenemia associated with long-standing intrauterine fetal death, *Amer. J. Obstet Gynec. 66*:500-06, 1953.
35. Bruton, O. C. Agammaglobulinemia, *Pediatrics 9*:722-28, 1952.
36. Bruton, O. C., Apt, L., Gitlin, D. and Janeway, C. A. Absence of serum gamma globulins, *A. M. A. Amer. J. Dis. Child. 84*:632-36, 1952.
37. Janeway, C. A., Apt, L. and Gitlin, D. Agammaglobulinemia, *Trans. Assoc. Amer. Phycns. 66*:200-02, 1953.
38. Barondess, J. A. Present status of gamma globulin, *Pediatrics 10*:732-42, 1952.
39. Stokes, J., Jr., Farquhar, J. A., Drake, M. E., Capps, R. B., Ward, C. S., Jr. and Kitts, A. W. Infectious hepatitis; length of protection by immune serum globulin (gamma globulin) during epidemics, *J. Amer. med. Assoc. 147*:714-19, 1951.
40. Brooks, B. F., Hsia, D. Y. and Gellis, S. S. Family outbreaks of infectious hepatitis; prophylactic use of gamma globulin, *New Engl. J. Med. 249*:58-61, 1953.
41. Hammon, W. M., Coriell, L. L. and Stokes, J., Jr. Evaluation of Red Cross gamma globulin as a prophylactic agent for poliomyelitis; plan of controlled field tests and results of 1951 pilot study in Utah, *J. Amer. med. Assoc. 150*:739-49, 1952; and Conduct and early follow-up of 1952 Texas and Iowa-Nebraska studies, *Ibid. 150*:750-56, 1952.
42. Hammon, W. M., Coriell, L. L., Wehrle, P. F., Klimt, C. R. and Stokes, J., Jr. Evaluation of Red Cross gamma globulin as a prophylactic agent for poliomyelitis; preliminary report of results based on clinical diagnoses, *J. Amer. med. Assoc. 150*:757-60, 1952.
43. Gellis, S. S., McGuiness, A. C. and Peters, M. Study on the prevention of mumps orchitis by gamma globulin, *Amer. J. med. Sci. 210*:661-64, 1945.
44. Cohn, E. J. Blood and blood deriva-

tives, *Amer. Scient. 33*:61-83, 1945.

45. Schade, A. L. and Caroline, L. An iron-binding component in human blood plasma, *Science 104*:340-41, 1946.
46. Koechlin, B. A. Preparation and properties of serum and plasma proteins; the beta$_1$-metal-combining protein of human plasma, *J. Amer. chem. Soc. 74*: 2649-53, 1952.
47. Cartwright, G. E. and Wintrobe, M. M. The anemia of infection; studies on the iron-binding capacity of serum, *J. clin. Invest. 28*:86-98, 1949.
48. Holmberg, C. G. and Laurell, C.-B. Investigations in serum copper; isolation of the copper containing protein and a description of some of its properties, *Acta. chem. scand. 2*:550-56, 1948.
49. Scheinberg, I. H. and Gitlin, D. Deficiency of ceruloplasmin in patients with hepatolenticular degeneration (Wilson's disease), *Science 116*:484-85, 1952.
50. Holmberg, C. G. and Laurell, C.-B. Investigations in serum copper; coeruloplasmin as an enzyme, *Acta. chem. scand. 5*:476-80, 1951.
51. Denny-Brown, D. and Porter, H. Effect of BAL (2, 3-dimercaptopropanol) on hepatolenticular degeneration (Wilson's disease), *New Engl. J. Med. 245*: 917-25, 1951.
52. Scheinberg, I. H. and Gitlin, D. *J. clin. Invest.*, in press.
53. Scheinberg, I. H. *J. clin. Invest.*, in press.
54. Rhoads, J. E. and Fitz-Hugh, T., Jr. Idiopathic hypoprothrombinemia — an apparently unrecorded condition, *Amer. J. med. Sci. 202*:662-70, 1941.
55. Owren, P. A. Parahemophilia; hæmorrhagic diathesis due to absence of a previously unknown clotting factor, *Lancet 1*:446-48, 1947.
56. Frank, E., Bilhan, N. and Ekren, H. Die Parahämophilie (Owren), eine neue Form der hämorrhagischen Diathese, *Acta haemat. 3*:70-90, 1950.
57. Alexander, B., Goldstein, R., Landwehr, G. and Cook, C. D. Congenital SPCA deficiency; hitherto unrecognized coagulation defect with hemorrhage rectified by serum and serum fractions, *J. clin. Invest. 30*:596-608, 1951.
58. Soulier, J. P. and Larrieu, M. J. Differentiation of hemophilia into two groups; a study of thirty-three cases, *New Engl. J. Med. 249*:547-53, 1953.
59. London, I. M. Studies on the rates of formation of serum proteins in man, in *Symposia on nutrition*, vol. 2, *Plasma proteins*, Springfield, Ill., Charles C. Thomas, 1950, pp. 72-82.
60. Whipple, G. H. and Madden, S. C. Hemoglobin, plasma protein and cell protein, *Medicine 23*:215-24, 1944.
61. Gitlin, D. and Janeway, C. A. Dynamic equilibrium between circulating and extravascular plasma proteins, *Science 118*:301-02, 1953.
62. Lindgren, F. T., Elliott, H. A. and Gofman, J. W. Ultracentrifugal characterization and isolation of human blood lipids and lipoproteins with applications to the study of atherosclerosis, *J. phys. Colloid Chem. 55*:80-93, 1951.
63. Russ, E. M., Eder, H. A. and Barr, D. P. Protein-lipid relationships in human plasma; in normal individuals, *Amer. J. Med. 11*:468-79, 1951.
64. Barr, D. P., Russ, E. M. and Eder, H. A. Protein-lipid relationships in human plasma; in atherosclerosis and related conditions, *Amer. J. Med. 11*:480-93, 1951.
65. Oncley, J. L. and Gurd, F. R. N. The lipoproteins of human plasma, in *Blood cells and plasma proteins; their state in nature*, edited by James L. Tullis, New York Academic Press Inc., 1953, pp. 337-57.
66. Eder, H. A. and Russ, E. M. Composition and distribution of plasma lipoproteins in normal and pathological states (abstract), *J. clin. Invest. 31*: 626, 1952.
67. Eder, H. A. Personal communication to the author.
68. Sperry, W. M. and Webb, M. Revision of the Schoenheimer-Sperry method for cholesterol determination, *J. biol. Chem. 187*:97-106, 1950.

BLOOD VOLUME IN HEALTH AND DISEASE*

SOLOMON A. BERSON

Assistant Director, The Radioisotope Unit,
Veterans Administration Hospital, Bronx, N. Y.

ALTHOUGH physiologic and pathologic alterations in circulating blood volume do not generally come within the purview of the hematologist, neither are they in the specific province of any other specialty. The subject of this presentation then may be appropriately considered in a program devoted to abnormalities of the blood.

Early interest in blood volume was expressed in its measurement by the exsanguination of condemned criminals. Aside from the fact that this method did not promise to be applied with much benefit at the bedside, its accuracy was open to question. Interestingly enough, in spite of considerable refinement in techniques, the accuracy of blood volume determinations still remains a matter of some dispute. It behooves us, therefore, to examine, in some detail, the manner in which blood volume is estimated, before considering what the estimations purport to reveal in the various clinical states.

Most recent methods have utilized the tracer dilution principle, wherein some detectable label is introduced into the blood stream and, after a suitable interval for mixing throughout the vascular system, its concentration is determined. For example, if five million units of label are injected and the concentration is found to be 1000/ml., after mixing, the apparent volume of dilution is 5000 ml.

Aside from nontoxicity, the label should have the following characteristics. It must remain within the vascular system for a time sufficient to insure complete mixing, it must not be destroyed during the same period and it must mix uniformly in the volume to be measured. If there is a leak out of the compartment or destruction within the compartment, the concentration of the label in the sample specimens will be lower than if it is entirely retained within the compartment and falsely high values for volume will result. If mixing is not uniform the samples will

* Presented at the 26th Graduate Fortnight of The New York Academy of Medicine, Oct. 30, 1953.

not be representative of the entire compartment and spuriously high or low values will be obtained. Herein lies one of the complexities of blood volume measurements to which we will return in a little while.

The labels which have been used to measure intravascular volume travel either with the erythrocytes or with the plasma. Many different red blood cell labels have been employed. The first of these was carbon monoxide,[1] which combines rapidly with hemoglobin. From the amount absorbed by the body and its concentration in blood samples its space of distribution was calculated by the dilution principle. Unfortunately, there is a leak in this system, some of the carbon monoxide leaving the blood stream and combining with myoglobin in muscle, thus leading to falsely high values for blood volume. The principle of differential agglutination was originated by Ashby[2] to study the life span of erythrocytes, and subsequently employed by other workers[3] to measure blood volume. In this method the erythrocyte label is blood of a different type than that of the subject's own cells. The labeled transfused cells can be counted in the withdrawn samples after antiserum has agglutinated the recipient's cells.

In recent years, a variety of radioisotopes have served as erythrocyte labels, including the two iron isotopes Fe^{55}, Fe^{59},[4, 5] P^{32},[6] K^{42}[7] and Cr^{51}.[8] The iron isotopes are inconvenient in that they have to be built into the cells by feeding radioiron to donors who bear the onus of repeated donation. The other isotopes mentioned can be used to tag the subject's own cells in vitro simply by incubation for an hour or two before injection. Total red blood cell volume determinations performed simultaneously with two of these tags, as has been done with P^{32} and K^{42},[7] give essentially identical values so that the same volume is being measured by these methods.

The plasma labels which have been most widely used are the Blue dye, T-1824[9] and more recently, radioiodinated serum proteins.[10-16] The dye molecule itself is small enough to pass through the capillary wall of the vascular compartment but it combines firmly with serum albumin,[17, 18] which leaves the blood stream quite slowly. While there may remain some debatable questions concerning the use of the dye in certain pathologic states,[19] recent measurements have shown that during the first fifteen minutes or so it distributes into essentially the same volume as that of bovine serum proteins,[20] certain polysaccharides[20] and radioiodine tagged human serum albumin.[13, 15, 16] Therefore it may be

accepted that either iodinated serum proteins or the Blue dye can be employed to measure the plasma volume reliably.

The early arterial time concentration curves, following injection of tagged cells or radioiodinated albumin, show an initial marked drop during the first minute or so, which is followed by a further fall in concentration of 5 to 10 per cent at most during the next five minutes for both iodoalbumin and tagged erythrocytes.[14] The variations for the next half hour or so, as shown by the venous concentrations are within the margin of technical error[14] but from more prolonged studies are deduced to be of the order of 4 to 5 per cent per hour. In the case of P^{32} or K^{42} tagged red cells, this loss in concentration is due to slow exchange with the plasma electrolytes and leak of the isotope out of the vascular compartment and in the case of I^{131} tagged albumin, to passage of the albumin molecule itself through the capillary wall.[21, 22] In heart failure where circulation is slowed, the early fall in concentration is more prolonged but at twelve to fifteen minutes, mixing has been completed nevertheless.[14] Studies with T-1824 have revealed the same findings.[9, 23] From these observations it is concluded that sampling at twelve to fifteen minutes insures complete mixing and that the required correction for loss from the blood stream during this time is only about 1 per cent.

In a number of studies,[3, 24-31] simultaneous experiments with tagged red cells and the Blue dye yielded values for erythrocyte and plasma volumes respectively which were not in agreement with the relationship between the two as determined by the centrifuge hematocrit reading. In these cases the relative cell volume calculated from the total erythrocyte volume divided by the sum of erythrocyte and plasma volumes was always lower than that obtained by centrifugation, by 10 to 12 per cent on the average. Theoretically, three possible causes for this apparent discrepancy are suggested. Two of these indict the methods as being in error while the third resolves the difficulty in physiologic terms.

Overestimation of relative cell volume by the hematocrit method would appear, at first, to be the simplest explanation. Since the packed cell column in the hematocrit tube contains some plasma trapped within it, the observed level of erythrocytes does not indicate the true relative cell volume but is actually in error by being too high, by as much as 9 to 10 per cent, according to some estimates.[32, 33] In fact, by applying such a large correction for trapped plasma, some investigators[34] were

able to adjust the centrifuge hematocrit readings sufficiently to bring them in line with the ratios obtained from the dilution studies. The problem of trapped plasma has recently been reinvestigated by the addition of a small amount of I^{131} tagged albumin to the whole blood and assay of the cell column and supernatant plasma for radioactivity.[35, 36] Careful studies by this method have demonstrated that the error of the hematocrit reading due to trapping of plasma in tubes spun at 2000 g for thirty minutes is not in excess of 2 per cent, and therefore does not satisfactorily account for the discrepancy in question. Furthermore, in simultaneous studies with I^{131} tagged albumin and tagged erythrocytes where whole blood samples were assayed for both, thus obviating any significant influence of possible errors in the centrifuge hematocrit readings, the same discrepancy was noted nevertheless.[14]

The second possibility which has been suggested is that some dye leaks out of the vascular system during the mixing period. Were this so, the true plasma volume accounting for this leak would be smaller than that calculated from the apparent dye dilution. The true ratio, $\frac{\text{red blood cell volume}}{\text{red blood cell volume} + \text{plasma volume}}$, might then actually equal the value obtained in the centrifuge hematocrit. Although studies with iodinated albumin and tagged red cells[14] showed essentially the same results as those utilizing the dye as a measure of plasma volume, the remote possibility remains that some moiety of both of these may rapidly enter some extravascular compartment during the early mixing period and thus lead to a measure of something more than true intravascular plasma volume. The liver has been suggested as the site of this early accumulation,[19] but if so, this leak with radioiodinated albumin must occur within the first minute, for after that time there is no detectable build up of radioactivity over the liver.[37] Furthermore, after the first minute no significant difference was observed between the arterial time concentration curves of tagged cells and tagged albumin during the mixing period.[14] Thus, while the possibility of such a leak from the intravascular circulation has not yet been completely excluded, there is no evidence to favor it.

At the present time, most workers accept the explanation first suggested by Smith, Arnold and Whipple[38] more than thirty years ago. It is conceded that the corrected centrifuge hematocrit is accurate and that the dilution techniques measure accurately total erythrocyte and

plasma volumes. The relative cell volume derived from these latter values may be termed the average relative cell volume of the body as opposed to that of peripheral large vessel blood which is measured in the centrifuge tube. Since the former is lower than the latter, the implication is that in some vessels the ratio of cells to the plasma is lower than in the blood which is obtained from a peripheral artery or vein. There is evidence that this low ratio exists in the minute vessels. Krogh[39] noted that such vessels are lined by a marginal layer of plasma through which an axial stream of blood flows. Fahraeus[40] demonstrated a similar phenomenon in capillary tubes and Gibson[10] observed a lower hematocrit in the minute vessels of most tissues than in the large vessels. It is evident that if plasma lines the endothelium of all vessels, the relative cell volume of the blood within the vessels will be significantly lower in those small enough for this juxtamural layer to comprise an appreciable moiety of the entire contents.

The situation may be represented as in Figure 1. The large compartment represents large vessel blood; the compartment with the low hematocrit represents minute vessel blood. In addition there is a small compartment composed of splenic blood which has a relatively high hematocrit, but which is not quantitatively important in normal man. Therefore, mixing of tagged erythrocytes and plasma is not uniform when referred to concentration in whole blood, and samples selected from the peripheral compartment are not truly representative of the entire pool. For this reason whole blood volume cannot be determined precisely from the dilution of tagged red cells or labeled plasma alone. Since the distributions of tagged red cells in the erythrocyte pool and of labeled albumin in the plasma pool are presumed to be uniform, each can be measured separately and the total volume calculated from the sum of the two. In a number of such determinations performed simultaneously the average relative cell volume of the body was found to average 92.5 per cent of the peripheral vessel hematocrit.[14] Similar relationships have been observed in studies utilizing the Blue dye and iron tagged erythrocytes.[26] If the mean value of .925 is taken as the average relative cell volume/peripheral vessel hematocrit ratio, calculation of total blood volume from albumin or erythrocyte dilution alone is not likely to be in error by more than about 7 per cent. However, this ratio may change under various physiological or pathological conditions and such calculations may then lead to larger errors.

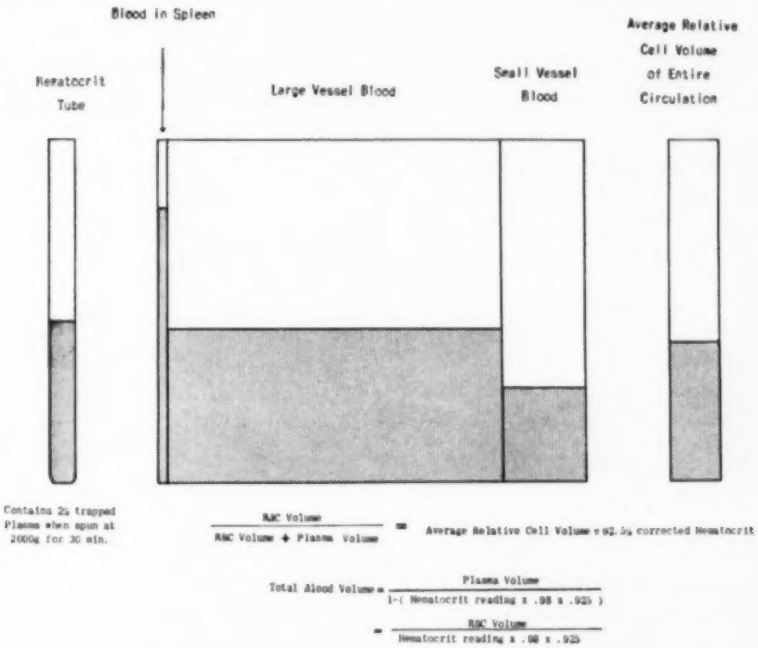

Blood in Spleen
Average Relative Cell Volume of Entire Circulation
Hematocrit Tube
Large Vessel Blood
Small Vessel Blood
Contains 2% trapped Plasma when spun at 2000g for 30 min.
RBC Volume / RBC Volume + Plasma Volume = Average Relative Cell Volume = 92.5% corrected Hematocrit
Total Blood Volume = Plasma Volume / 1-(Hematocrit reading x .98 x .925)
= RBC Volume / Hematocrit reading x .98 x .925

Figure 1
Relative amounts of plasma and erythrocytes in various parts of the circulation. Comparison of average relative cell volume of entire circulation with the hematocrit value of peripheral large vessel blood.

Plasma volume (P.V.) is determined from the dilution of I^{131} labeled human serum albumin (or the dye T-1824).

$$\text{P.V.} = \frac{\text{Total radioactivity injected}}{\text{Radioactivity/ml plasma}}$$

Red Blood cell volume (R.B.C.V.) is determined from the dilution of P^{32} (or other) labeled erythrocytes.

$$\text{R.B.C.V.} = \frac{\text{Total radioactivity injected}}{\text{Radioactivity/ml R.B.C.}}$$

The total blood volume may be approximately calculated from the dilution of either tagged albumin or erythrocytes alone according to the formulae given in the figure.

The whole blood concentration of radioactivity following intravenous administration of P^{32} tagged erythrocytes to a subject at bed rest and in the "steady state" falls exponentially for about forty-eight hours or so with a half time averaging about twenty-four hours.[41] The departure from a constant decay rate after this time is related to a number of factors which do not merit discussion at this point. However, the period of exponential

TABLE I—NORMAL VALUES FOR PLASMA VOLUME AND RED BLOOD CELL VOLUME AS GIVEN IN THE LITERATURE

Method	*ml/kg body weight*	*Reference*
	Plasma Volume	
T-1824	43.08	(23)
T-1824	44.7	(68)
T-1824	46.6	(28)
I^{131} Alb.	40.2 (male subjects)*	(127)
	Red Blood Cell Volume	
Fe^{59} or Fe^{59} tagged cells	29.7 (male subjects)	(26)
P^{32} " "	30.0	(28)
P^{32} " "	29.9 (male subjects)	(128)
P^{32} or K^{42} " "	28.7 (male subjects)*	(127)

* Hospital subjects free from diseases of the blood, cardiovascular system, liver and kidneys. The group includes patients with psychoneurosis, localized eye disturbances, nonbleeding duodenal ulcer and some without known disease.

decay may be used to quantitate changes in blood volume in acute experiments, thus avoiding the onerous techniques of repeated reinjection and resampling. After the straight line is established by observations during a control period, expansion of plasma volume leading to hemodilution is indicated by a fall in P^{32} concentration below the extrapolated portion of this line. Conversely, hemoconcentration resulting from contraction of plasma volume is indicated by the P^{32} concentration falling above the line. Although this method ignores possible shifts in the ratio between average cell volume and the peripheral vessel hematocrit, it has proven very useful in following serial changes for periods of twenty-four hours or so.[41]

Excellent critical discussions of techniques and methods are to be found in the recent reviews of Reeve,[42] Mollison[43] and Gregersen.[44]

PHYSIOLOGICAL VARIATIONS

In normal subjects red cell volume comprises about 3 per cent and plasma volume a little over 4 per cent of body weight (Table I). However, since muscle contains relatively more blood than fat, it has been observed[22] that, when related to weight, values for obese subjects are lower than for lean subjects. The somewhat lower values obtained in our series with I^{131} albumin may be due to the fact that our hospital subjects

are not as muscular as the medical students chosen for several of the other normal groups. However, some part of the difference may actually owe itself to the dye having a slightly greater space of distribution than the tagged albumin. The studies referred to previously,[15, 16] in which simultaneous dye and iodinated plasma volumes were performed, showed an average space of distribution only 2 per cent greater with the dye, at least after the first circulation through the tissues. However, the undialyzed albumin preparations used in these studies uniformly contained approximately 3 per cent nonprotein bound radioactivity[14, 22, 35] so that it remains quite possible that our plasma volumes with I^{131} tagged albumin are in fact some 4-5 per cent lower than those obtained with the dye.

Change in body weight induced by overeating or dieting[45] leads to little alteration in circulating blood volume. Even during moderately severe caloric starvation the blood volume remains constant in absolute figures, thus increasing greatly in relation to body weight.[46] Our own observations in patients with weight loss from chronic disease likewise show abnormally high values per kilogram body weight. A closer correlation with height has been suggested by some,[23] but has not been found to be significant by others.[47] Gregersen and Nickerson[47] have attempted a correlation with body type but found this to be of value only in extreme cases. In normal subjects the rather wide range of individual variations whether related to height, weight or surface area (coefficient of variation about $\pm$ 10 per cent[47]) limits the application of average values to individual cases except where extreme abnormalities are present.

There is reported to be a slight seasonal variation, the blood volume increasing slightly in hot damp weather.[48] Persons living at high altitudes have an increased red cell volume[49] and rats maintained for eight days in a decompression chamber at simulated altitudes of 15-20,000 feet, show about a 100 per cent increase in red cell volume which is accompanied by a compensatory reduction of plasma volume.[50] There is a slight decrease in plasma volume during exercise[51, 52] and following the injection of adrenalin.[50] Under these conditions there is no appreciable change in red cell volume.[51-53] Pregnancy is associated with a rather striking increase in plasma volume which returns to normal during the first week postpartum.[54]

The alterations in blood volume induced by postural changes are of importance from several points of view. A fall in plasma volume with

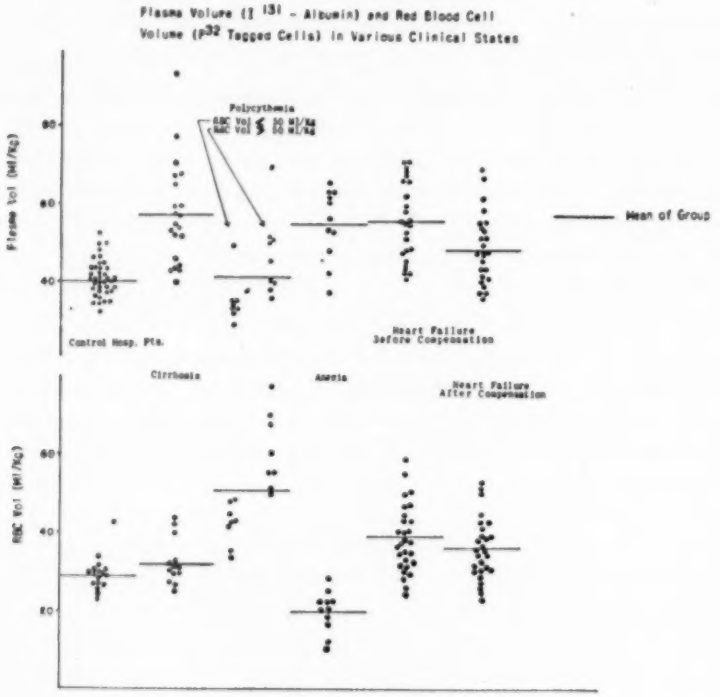

Plasma Volume (I 131 - Albumin) and Red Blood Cell Volume (P32 Tagged Cells) in Various Clinical States
Plasma Vol (ml/Kg)
RBC Vol (ml/Kg)
Polycythemia
Mean of Group
Control Hosp. Pts.
Heart Failure Before Compensation
Cirrhosis
Anemia
Heart Failure After Compensation

Figure 2—Blood volume in various clinical states.

With moderate elevation of R.B.C. volume in polycythemia, plasma volume decreases as a part of the homeostatic regulation of total blood volume. With greater increases in R.B.C. volume, plasma volume must also increase if excessive hemoconcentration and increase in viscosity are to be prevented.

In chronic anemia, plasma volume increases as a part of the homeostatic regulation of total blood volume.

In heart failure plasma volume and red cell volume are increased. The plasma volume decreases rapidly with compensation.

resulting hemoconcentration in the erect position and converse changes in recumbency have been repeatedly confirmed.[41,55,56] Cardiac patients may show as much as a 15-20 per cent increase in blood volume within an hour or two after lying down.[41] In addition, redistribution of blood with shift into the pulmonary bed is thought to occur in recumbency[57,58] although this has been denied.[59] These changes contribute to the symptoms of orthopnea and paroxysmal nocturnal dyspnea and explain the

therapeutic effectiveness of orthostasis, phlebotomy and the application of tourniquets.

Because of the striking postural effects on blood volume, determinations should be performed under nearly "basal" conditions.

Pathologic States

Primary Disturbances of Red Cell Volume: The chief disturbances in red cell volume are represented in the polycythemias and the chronic anemias. In polycythemia vera there is an unknown factor operating to increase the rate of red blood cell formation. In the various secondary polycythemias the common denominator is presumed to be the stimulus of hypoxia. Since there is no normal mechanism for getting rid of excess blood cells, the total red cell volume increases in these conditions. In the presence of moderate elevation of circulating erythrocyte volume there is frequently a compensatory decrease in plasma volume[60,61] (Fig. 2), and total blood volume is maintained near normal levels. However, with further increase in red cells the plasma volume must also rise (Fig. 2) if excessive hemoconcentration and increase in viscosity are to be prevented. Following repeated phlebotomy in long standing polycythemia, the plasma volume frequently continues to increase sufficiently to maintain total blood volume at levels considerably above normal.[62] Apparently, the marked increase in vascular bed, once established and sustained for a long period of time, cannot immediately contract back to normal. Eventually, following continued therapy, normal blood volume values may be realized.

In the anemias, the maintenance of circulating volume is effected through an increase in plasma volume[60] (Fig. 2), occasionally sufficient to increase total blood volume to high normal levels. The more severe the anemia, the more prominent is the elevation of plasma volume. Following successful antianemic therapy, plasma volume returns rapidly to normal.[63]

Primary Disturbances of Whole Blood Volume: A sudden decrease in total blood volume resulting from phlebotomy or internal or external hemorrhage, is at first corrected by expansion of plasma volume alone, there being no immediately available reserve stores of erythrocytes.[10,51,64] When only slight or moderate blood losses have been incurred, full compensation and even transient overcompensation may be observed[41,65] but the response is quite variable.[65] With more severe acute

losses, the failure of compensation leads to the syndrome of clinical shock.

In cases of shock resulting from hemorrhage or skeletal trauma, the blood volume is reduced at least 30 to 40 per cent below normal.[66,67] The severity of the clinical syndrome parallels closely the reduction in circulating blood volume, which in turn is dependent upon the extent of blood loss at the sites of trauma. The falls in hematocrit and hemoglobin concentration indicate a compensatory increase in plasma volume resulting from absorption of interstitial fluid into the circulation. There is considerable evidence against the now obsolete theory of generalized increase in capillary permeability to plasma proteins in traumatic,[68] burn,[69] or hemorrhagic[66] shock.

In cases of burns and abdominal injury with peritonitis,[66] there is often hemoconcentration, owing to selectively greater plasma loss at the sites of injury, and a marked shift of sodium chloride into cells in the burned areas.[70] This explains the beneficial results attributed to sodium chloride in burn shock[71,72] as compared to its relative ineffectiveness in hemorrhagic shock.[73]

Plasma Expanders: Pertinent to the subject of hemorrhagic shock is the consideration of the so-called blood substitutes. There is no disputing that when blood has been lost there is no completely satisfactory substitute. However, there is great need for suitable substances as temporizing first aid measures until whole blood transfusions can be given. These substances have become known as plasma expanders or plasma extenders and aid in the restoration of circulating plasma volume by drawing fluid into or holding fluid within the blood stream by virtue of their oncotic pressure. Under emergency conditions, the plasma expanders may even have certain definite potential advantages over whole blood. Aside from greater availability, easier storage and stock piling, use of these substances obviates the need for typing and cross matching and eliminates concern over transfusion reactions.

The effect of small molecules on plasma volume is virtually negligible because of rapid passage through the capillary wall. When physiological saline solution is given intravenously it tends to distribute itself rapidly throughout the entire volume of extracellular fluid. Tracer studies with radioactive Na^{24} reveal that dilution in a volume equal to that of extracellular fluid is effected within 15 minutes.[74] When extracellular fluid volume is large as in edematous states, 500 ml. isotonic saline solution given

intravenously over a short period of time, fails to produce a detectable increase in plasma volume.[41] Even when larger amounts are given in the absence of edema, plasma volume is usually increased by only about 1/4 to 1/5 of the administered volume, and this increase is quite transient. Following blood loss, the improvement brought about by sodium chloride is little if any greater than that which occurs spontaneously by compensatory shifts of interstitial fluid into plasma.[64] In normal subjects, after moderate acute blood loss, there is no deficit of the interstitial fluid to limit this process. However, in surgical patients who may have a diminished interstitial fluid volume due to dehydration, an adequate supply of saline is indicated to permit compensatory restoration of plasma volume.[75] Where there is a specific deficiency of sodium, as in burns[70,71] and salt depletion shock,[76] physiological saline alone may bring about rapid and striking restoration of plasma volume, but even in these cases smaller amounts of salt-containing plasma may be more effective.[76]

Glucose is even less effective than saline as a plasma extender owing to its rapid excretion and its ability to penetrate cells and, therefore, to distribute in the whole of body water. A rapid intravenous infusion of 1000 ml. of 5 per cent glucose may produce no discernible increase in plasma volume.[37]

The plasma extenders on trial at present comprise a group of protein and carbohydrate substances with molecular weights beginning at about 30,000. Globin derived from human erythrocytes has been suggested as a plasma extender.[77] Since a volume of whole blood yields approximately 2½ times as much globin as albumin without sacrifice of the latter, a fairly large, though limited, source of supply is available. Unfortunately, because of the relatively small molecular size of this protein (m.w., 34,000), it is lost rapidly from the blood stream. In addition, globin is quickly metabolized, probably by the liver[37] and only about one-third remains intravascularly at the end of a one and a half hour infusion. Its effectiveness as a plasma expander, therefore, is definitely limited, as confirmed by blood volume studies.[37] Investigations with tracer doses of radioiodinated human serum albumin (m. w., 69,000) reveal a net rate of loss from plasma of only about 5 per cent per hour. About 60 per cent of the tracer remains intravascularly at the end of twenty-four hours.[21,22] Clinical studies[78] confirm theoretical predictions[79] that 1 gram of albumin holds approximately 18 ml. of fluid within the blood vessels by virtue of its oncotic pressure. Thus, 25 grams of albumin expands blood volume

roughly to the same extent as 500 ml. of plasma and has the additional advantage of freedom from the risk of transmitting virus hepatitis.

The gelatins, derived from degradation of bone and skin collagen, have been widely investigated and found to effectively increase plasma volume.[80] Most gelatins are of high viscosity and solidify under refrigeration. A preparation containing smaller molecules of m.w. 30-40,000, known as oxypolygelatin, with a gel point at 10°-13° C in 6 per cent solution[81] is less salutary in its effect on plasma volume[73] probably because of rapid loss through the capillaries. Within fifteen minutes after completion of an infusion, approximately one-third has left the blood stream and at the end of four hours only one-third remains in the circulation.[82] Antigenicity has not been demonstrated with the gelatins but difficulty in typing and cross matching is experienced following gelatin infusions.

The nonprotein macromolecular substances under current scrutiny are dextran and polyvinyl pyrollidone. The former is a glucose polysaccharide, produced by enzymatic action of Leuconostoc mesenteroides in sucrose. The resulting long chain product with a molecular weight of several millions is then degraded by acid hydrolysis. Fractional precipitation with acetone yields a large fraction of molecules about the molecular weight of serum albumin, but with a wide range of smaller and larger particles also present. It effectively elevates plasma volume in normal and blood depleted subjects,[83] and is apparently not stored for prolonged periods, as shown by the recovery of two-thirds the intravenously administered dose of C^{14} labeled dextran in the urine within three days.[81] Reactions to American dextran have been much less frequent and less severe than reactions to Swedish dextran. However, there is a tendency to antigenicity[83] and to cross reactivity with naturally occurring antibodies,[80, 83] which may prove to be problems in the future.

Polyvinyl pyrollidone (PVP) is a colloid produced through the combination of formaldehyde and acetylene. The imported products have molecular weights of about 40,000 as compared to 65-70,000 for the PVP-macrose supplied by Schenley Laboratories. The latter has been shown to be more effective in producing survival of severely bled animals.[73]

From a number of different lines of evidence it is probable that effective plasma expanders will not be found much below a molecular weight of about 35,000-40,000, which appears to be at about the threshold for

rapid transcapillary passage. However, other factors, such as shape, may modify the molecular weight level at which rapid loss from the blood stream occurs.

Most of the plasma expanders discussed have shown some evidence of transient storage in tissues and the production of minor pathologic changes in experimental animals has been reported,[73] but, with the exception of some temporary depression of T_mPAH following dextran,[81] definite functional impairment has not been demonstrated.

Primary Disturbances of Plasma Volume: The chief conditions of interest with respect to abnormal plasma volume per se are heart failure, cirrhosis of the liver, and the nephrotic syndrome.

A number of dye plasma volume studies[84-86] are in agreement as to the presence of an increased blood volume in most cases of chronic congestive heart failure. However, several recent reports based on tagged red cell estimations[87-89] have failed to confirm these findings with the contention that the dye method is grossly in error in this condition. We have recently performed simultaneous P^{32} tagged red cell and radioiodinated albumin plasma volumes in twenty-six cases of heart failure before and after compensation was restored by active therapeutic measures.[90] The results of these studies appear to resolve the disagreement just noted. Red blood cell volumes determined by the P^{32} cell method showed moderate elevation above normal and a slight decrease following compensation. When plasma volumes were calculated solely from the red cell volumes and the hematocrit readings, the apparent changes following compensation were relatively unimpressive. However, plasma volumes determined directly by the I^{131} albumin method were found to be elevated considerably above normal and to decrease, often strikingly, with compensation (Fig. 2). The reason for this difference is to be found in an increase in the ratio, $\frac{\text{relative cell volume}}{\text{peripheral hematocrit value}}$, following compensation. These studies emphasize what has been noted previously, that accurate evaluation of erythrocyte and plasma volumes requires independent determinations of each.

With strenuous diuretic therapy of heart failure an acute loss of plasma volume, and resulting hemoconcentration, has been noted.[41] A marked decrease in red cell volume is not to be expected within a short time following treatment of heart failure, since disposal of the extra cells (presumably formed through the stimulus of hypoxia) is most likely

effected simply through a decrease in formation concurrent with a normal attrition rate. Although the life span of erythrocytes following compensation in heart failure has not been studied, there is no good evidence of an increased rate of destruction at that stage, and it has been demonstrated in rats that red cells formed following acclimatization to low atmospheric pressure, have a normal life span after return to sea level conditions.[91] We must conclude that decrease in production is the only normally available mechanism for disposal of excess red blood cells. Since the average normal life span for human erythrocytes is about 120 to 130 days,[43] a fall in red cell volume in excess of about 5 per cent per week is not to be anticipated following compensation, even if new cell formation were completely inhibited.

Low red blood cell counts and decrease in hemoglobin concentration are often observed in decompensated cirrhosis. Plasma volumes are often increased strikingly above normal levels (Fig. 2). In view of the increase in plasma volume noted in anemia, it might be suspected that the high plasma volume of decompensated cirrhosis is merely secondary to a decrease in red cell volume. However, direct measurements show that total red cell volume is usually essentially normal (Fig. 2), suggesting that the plasma volume increase is primary. The total blood volume is therefore elevated, and it may be concluded that the increment is accommodated chiefly in the increased vascular beds drained by the portal system and its collaterals. These findings have also been observed by others.[92, 93]

In the nephrotic syndrome, plasma volume is usually normal or only slightly diminished, although red cell volume may be subnormal and account for a decrease in total blood volume.[94] When the hypertensive stage with heart failure supervenes, plasma volume usually increases.

Homeostatic Regulation of Blood Volume

From observations of the compensatory changes which follow acute blood loss as well as those operating in chronic anemia and polycythemia, it seems clear that there are homeostatic mechanisms which maintain the total volume of blood within certain limits. It has already been indicated, that owing to the nonexistence of red blood cell reservoirs and the absence of normal mechanisms for rapid destruction of erythrocytes, changes in red cell volume can only be brought about by the slow processes of inhibition or acceleration of production. Therefore, early rapid compensation for increase or decrease in total blood volume must

be brought about by appropriate changes in plasma volume alone. These compensatory mechanisms can best be interpreted through consideration of the factors governing net fluid exchange in capillaries. According to the Starling hypothesis, outward filtration of fluid with resulting loss from the blood stream is promoted by the intracapillary hydrostatic pressure. Absorption of fluid from interstitial spaces and consequent increase in intravascular volume is favored by the effective oncotic pressure of the plasma proteins aided by the interstitial fluid tension. Normally the balance of these opposing factors maintains the proper plasma-interstitial fluid volume relationships. The decrease in blood volume which results from hemorrhage is responsible for a number of compensatory cardiovascular adjustments. Reflex arteriolar constriction serves to maintain arterial pressure in the presence of a diminished circulating blood volume. In dogs subjected to hemorrhage, arterial blood pressure is maintained at near normal levels until cardiac output falls to about 60 per cent of normal, indicating a widespread increase in peripheral vascular resistance through arteriolar constriction.[95] Where a decrease in plasma volume alone is produced by intraperitoneal administration of glucose, a high arterial pressure in the presence of a low cardiac output signifies a similar increase in peripheral resistance.[96] Direct observation of the omental blood vessels provides confirmation of this arteriolar constriction in the early stages of hemorrhagic shock.[97] A fall in intracapillary hydrostatic pressure is one of the results of arteriolar constriction and favors the absorption of interstitial fluid into the blood stream,[98] thus serving to bring about compensatory expansion of plasma volume. It is generally agreed that there is widespread increased peripheral resistance in the early stages of hemorrhagic shock,[99] and the low hematocrit levels observed in shocked patients[100] attest to the spontaneous compensatory increases in plasma volume. However, psychic and emotional factors tend to exert important influences on the neurovascular reactions, and may account for the failure to obtain evidence of increased peripheral resistance[101] or significant rapid restoration of blood volume[64] in experimental hemorrhage in human volunteers. The process of compensation is limited by the diluting effect on plasma proteins which results in a lowering of effective oncotic pressure.[64] Further compensation then demands an increase in plasma protein concentration. Extravascular stores of serum albumin amount to about 1 ½ times that circulating in the blood stream,[21,22] and within a few hours following loss of

circulating plasma protein, mobilization of this extravascular reserve is evidenced by an increase in total circulating albumin and further restoration of plasma volume.[64] This is probably effected through normal transfer mechanisms in the establishment of a new equilibrium ratio between intra- and extravascular albumin. Subsequent improvement in plasma albumin content is slow and occurs through increased production by the liver which is probably stimulated by the lowered plasma protein concentration.[102]

Following the infusion of solutions which tend to increase plasma volume, compensatory changes occur in the opposite direction. Cardiac output increases[103, 104] and arteriolar dilation produces a fall in peripheral resistance,[104, 105] thus leading to increase in intracapillary pressure and outward filtration of fluid.

Whether such hemodynamic factors, operating in less dramatic fashion, are likewise responsible for the compensatory changes in plasma volume which occur in most cases of chronic anemia and polycythemia, can only be suggested. The fact is that the body maintains total circulating volume at near normal levels in the presence of severe depletion or marked excess of total erythrocyte mass.

Ideas concerning the cause of hypervolemia in heart failure have been related to changing concepts of the genesis of edema in this condition. The "backward failure" theory, supported by the studies of Starling,[104] holds that venous pressure increases as an immediate and direct result of cardiac failure.* Although others[19, 105-107] have considered the damming back of blood in the venous system to be chiefly responsible for the expression of fluid into the interstitial spaces with the production of edema, Starling himself regarded the early compensatory changes resulting from inadequate blood flow as leading to vasoconstriction and fall in intracapillary hydrostatic pressure, thus favoring movement of fluid from extravascular spaces into the blood stream. He felt that subsequent stasis and anoxia contributed to an increase in capillary permeability,

* Some contemporary protagonists of the backward failure school[19, 106] attribute to Starling the view that increased venous pressure leading to increased capillary pressure is chiefly responsible for edema formation in heart failure. It is in the interests of historical accuracy to point out that Starling emphatically denied this sequence of events and referred to experiments which demonstrated the formation of edema in the absence of elevation of capillary pressure.[104] Starling also emphasized the necessity for postulating an increase in blood volume in order to account for high venous pressure in the presence of normal arterial pressure and further pointed out the significant roles of reduced cardiac output and renal blood flow and the influence of salt intake in the production of edema, all of which factors were subsequently incorporated into the modern "forward failure" theory. It would seem, therefore, that Starling's views are not to be regarded as being defended by today's members of the "backward failure" school nor as being opposed by those favoring modern concepts of forward failure. It should rather be conceded that Starling foresaw, some forty-five years ago, the potential significance of many factors enjoying a renaissance of interest today.

which in turn was at least partly responsible for the formation of edema. He concluded that not the increase in venous pressure nor any other single factor alone could satisfactorily account for the edema. The failure to find increased protein concentrations in extravascular fluid[108,109] has led generally to the abandonment of the altered permeability theory although Smirk[108] has argued that there may still be an increased permeability to water and crystalloids.

A large body of evidence has been marshalled against the concept that the edema of heart failure is a direct consequence of the elevated venous pressure which itself is a direct result of the inability of the injured myocardium to pump along the returning venous blood. Starr[110] failed to observe any conspicuous increase of venous pressure after severe acute experimental myocardial injury, and Warren and Stead[111] noted that the formation of edema occasionally preceded a rise in venous pressure. Even after death when the heart is no longer functioning, there is a higher static venous pressure in cardiac subjects as opposed to noncardiac subjects[112] which suggested the importance of increased blood volume as a cause of increased venous pressure in heart failure. These observations led to the revival of the forward failure theory.[110,111] This hypothesis regards the fall in output of the failing heart as the initiating factor in a sequence of events which leads, through a fall in renal blood flow,[113] to sodium and water retention and edema formation. The increase in interstitial fluid tension produced by the edema presumably then promotes movement of fluid into the capillaries which results in hypervolemia.[111] The increase in plasma volume is held primarily responsible for the elevation of venous pressure.[111,112]

Following experimental cardiac injury in dogs, Landis[107] also noted that venous pressures were usually normal at rest. However, he demonstrated that forced exercise led to increases in venous pressure in these animals. However, normal dogs showed a fall in venous pressure with exercise which was not halted by marked expansion of blood volume produced by massive transfusions. Landis concluded that the elevation of venous pressure in heart failure is a direct result of the myocardial injury and not of the increased blood volume. He suggested that intermittent increase in venous pressure produced by muscular effort in cardiac subjects is responsible for edema formation even in early cases where resting venous pressure may be normal. The resulting fall in plasma volume and compensatory vasoconstriction are presumed to stimu-

late the kidneys to retain salt and water. The postulated sequence of events here does not satisfactorily explain why reabsorption of fluid from tissue spaces does not occur immediately following cessation of exercise and also why marked increases in blood volume are ever observed. It would seem to follow that blood volume should only be low or, when restored by sufficient salt and water retention, normal. Moreover, Kaltreider and Meneely[114] noted similar increases in venous pressure in normal and cardiac subjects following exercise. Slight decreases in plasma volume occurred in both groups.

Further evidences submitted by the adherents of the backward failure hypothesis are the demonstration of an immediate increase in venous pressure in acute heart failure produced by diffuse cardiac damage[115] and the observation that increased venous pressure may precede formation of edema in cardiac patients deprived of digitalis.[116] It has also been demonstrated that high venous pressure per se can cause renal salt and water retention.[117]

Regardless of the precise order of events in heart failure, the total volume of extracellular fluid is dependent upon the relative intake and excretion of salt and water. Whether salt and water retention is primarily a result of low cardiac output or elevated venous pressure or both, the distribution of the retained fluid between plasma and interstitial spaces must be determined by factors regulating net transcapillary exchange. There is no denying a marked increase in capillary pressure in late stages as directly observed by Fahr and Ershler.[106] Furthermore, in order to explain why these high pressures do not lead to dehydration of the blood, one must grant an increase in the opposing force of interstitial fluid tension[118] produced by the edema in the absence of significant changes in effective oncotic pressure. The importance of an increased extravascular pressure limiting outward filtration from the blood stream in certain conditions cannot be neglected. For example, the inhibiting influence of ascitic fluid pressure on continued accumulation of ascites is emphasized by the sudden loss of fluid from the blood stream, with resulting rapid hemoconcentration, immediately following paracentesis.[41] However, observations at an advanced stage of heart failure when there is already marked expansion of both interstitial fluid and plasma volumes, do not aid in interpreting the importance of early causative factors. The idea that increase in blood volume is dependent solely upon a preexisting increase in interstitial fluid pressure ignores the frequently observed

hypervolemia in congestive heart failure,[90] polycythemia,[62] arteriovenous fistulas[119] and occasional cases of hepatic cirrhosis[62] without detectable edema. Although blood volumes fell with treatment in our cases of heart failure, they remained at supernormal levels even in the absence of edema.[90] It thus appears that an increase in blood volume is not necessarily dependent upon a prior increase in extracapillary pressure.

It has already been indicated that a decrease in intracapillary pressure is responsible for compensatory increase in plasma volume in hemorrhagic shock. A decrease in intracapillary pressure must also occur in the early stages of congestive heart failure as a result of the fall in cardiac output since arterial blood pressure is maintained at normal levels through arteriolar constriction. Most cases of chronic congestive failure show evidence of a marked increase in peripheral resistance which falls abruptly with successful digitalis therapy.

The hypothesis presented here thus postulates an increase in plasma volume at the expense of interstitial fluid as an early change in heart failure, prior to, coincident with or subsequent to and, in part, independent of renal salt and water retention. The presence of an increased blood volume in the absence of edema or elevation of venous pressure is consistent with this thesis. The difficulty of establishing these mechanisms in early failure is obvious, and interpretations based on changes which are observed in recovery from failure are fraught with complications. We attempted to evaluate fluid shifts between interstitial fluid and plasma compartments following digitalis therapy of heart failure.[41] According to the sequence postulated by backward failure theorists, the fall in venous pressure produced by digitalis should favor fluid absorption and hemodilution which would then stimulate diuresis. However, serial blood volume estimations at frequent intervals for forty-eight to seventy-two hours following digitalization failed to reveal hemodilution in any stage.[41] The first change noted was an increased urine output and this was followed by progressive hemoconcentration. The decrease in plasma volume was accounted for by the water loss in diuresis and it could not be concluded that plasma volume decreased as a result of passage of fluid into the interstitial space following an increase in cardiac output. More detailed measurements of simultaneous changes in total extracellular fluid and plasma volume are indicated. Although the experiments revealed that diuresis preceded any change in blood volume, the relative im-

portance of diminished glomerular filtration or renal blood flow and increase in renal venous pressure remains unresolved.

It must not be supposed that any of the theories presented fails to recognize the importance of many other factors. The extent and distribution of edema as well as fluctuations in plasma volume are influenced by the additional effects of gravity, exercise and the quantitative intake of salt.

In certain conditions, such as arteriovenous fistulas[120] and thyrotoxicosis,[121] an increase in blood volume is characteristically associated with a high cardiac output. The thyroidal I^{131} clearance values observed in severe thyrotoxicosis[122,123] indicate blood flows of one to 3 liters a minute to the thyroid alone. However, in these states the increases in blood volume and cardiac output are both the compensatory result of a diversion of blood flow away from the tissues in general, where the intracapillary hydrostatic pressure may be quite low. This is confirmed by the findings of marked generalized vasoconstriction and normal or low mean arterial pressure in large experimental arteriovenous fistulas in dogs.[124] The stimulus for increased plasma volume may then coexist with a high cardiac output. Although there is no relationship between blood flow and blood volume in specific tissues, blood flow in general may be markedly affected by changes in total blood volume, as, for example, in hemorrhagic shock where the blood flow to certain organs (e.g., kidneys) may be profoundly diminished as a consequence of inadequate circulating blood volume.

Although this discussion has been confined to a consideration of total circulating blood volumes, the possible importance of volume fluctuations in certain local areas independent of changes in the general circulation is becoming increasingly apparent. Thus, variations of the pulmonary blood volume are held responsible for a regulatory effect on renal water excretion.[125] Renal sodium excretion is presumed to be controlled in part by changes in cranial blood volume.[126] Other unknown sectors have also been suggested as acting as volume indicators to which the kidneys are sensitive[105] directly or indirectly. Further detailed discussion of this interesting subject is beyond the scope of this presentation, but it is well to point out that the field of specific local alterations in blood remains, at present, virgin soil, a virtually unexplored realm of investigation for those who are not discouraged at the large number of entries already included in the book of blood volume studies.

REFERENCES

1. Haldane, J. S. and Smith J. L. The mass and oxygen capacity of the blood in man, *J. Physiol. 25*:331-43, 1900.
2. Ashby, W. The determination of the length of life of transfused blood corpuscles in man, *J. exp. Med. 29*:267-81, 1919.
3. Barnes, D. W. H., Loutit, J. F. and Reeve, E. B. A comparison of estimates of circulating red blood cell volume given by Ashby marked red cell method and T-1824 hæmatocrit method in man, *Clin. Sci. 7*:135-54, 1948.
4. Hahn, P. F., Balfour, W. M., Ross, J. F., Bale, W. F. and Whipple, G. H. Red cell volume circulating and total as determined by radio iron, *Science 93*:87-88, 1941.
5. Gibson, J. G., II, Weiss, S., Evans, R. D., Peacock, W. C., Irvine, J. W., Jr., Good, W. M. and Kip, A. F. Measurement of circulating red cell volume by means of 2 radioactive isotopes of iron, *J. clin. Invest. 25*:616-26, 1946.
6. Hahn, L. and Hevesy, G. A method of blood volume determination, *Acta physiol. scand. 1*:3-10, 1940.
7. Yalow, R. S. and Berson, S. A. The use of K^{42} tagged erythrocytes in blood volume determinations, *Science 114*:14-15, 1951.
8. Gray, S. J. and Sterling, K. Determination of circulating red cell volume by radioactive chromium, *Science 112*: 179-80, 1950.
9. Gibson, J. G., II and Evans, W. A., Jr. Clinical studies of the blood volume; clinical application of a method employing the azo dye "Evans blue" and the spectrophotometer, *J. clin. Invest. 16*:301-16, 1937.
10. Gibson, J. G., II, Seligman, A. M., Peacock, W. C., Aub, J. C., Fine, J. and Evans, R. D. The distribution of red cells and plasma in large and minute vessels of the normal dog, determined by radioactive isotopes of iron and iodine, *J. clin. Invest. 25*: 848-57, 1946.
11. Krieger, H., Storaasli, J. P., Friedell, H. L. and Holden, W. D. A comparative study of blood volume in dogs, *Proc. Soc. exp. Biol. Med. 68*:511-15, 1948.
12. Storaasli, J. P., Krieger, H., Friedell, H. L. and Holden, W. D. The use of radioactive iodinated plasma protein in the study of blood volume, *Surg. Gynec. Obstet. 91*:458-64, 1950.
13. Crispell, K. R., Porter, B. and Nieset, R. T. Studies of plasma volume using human serum albumin tagged with radioactive iodine, *J. clin. Invest. 29*:513-16, 1950.
14. Berson, S. A. and Yalow, R. S. The use of K^{42} or P^{32} labeled erythrocytes and I^{131} tagged human serum albumin in simultaneous blood volume determinations, *J. clin. Invest. 31*:572-80, 1952.
15. Schultz, A. L., Hammarsten, J. F., Heller, B. I. and Ebert, R. V. A critical comparison of the T-1824 dye and iodinated albumin methods for plasma volume measurement, *J. clin. Invest. 32*:107-12, 1953.
16. Freinkel, N., Schreiner, G. E. and Athens, J. W. Simultaneous distribution of T-1824 and I^{131} labeled human serum albumin in man, *J. clin. Invest. 32*:138-48, 1953.
17. Rawson, R. A. Binding of T-1824 and structurally related diazo dyes by the plasma proteins, *Amer. J. Physiol. 138*: 708-17, 1943.
18. Allen, T. H. and Orahovats, P. D. Combination of tolidine dye isomers with plasma albumin, *Amer. J. Physiol. 161*:473-82, 1950.
19. Peters, J. P. The role of sodium in the production of edema, *New Engl. J. Med. 239*:353-62, 1948.
20. Gregersen, M. I., Bayden, A. A. and Allison, J. B. Direct comparison in dogs of plasma volume measured with T-1824 and with antigens, *Amer. J. Physiol. 163*:517-28, 1950.
21. Sterling, K. The turnover rate of serum albumin in man as measured by I^{131} tagged albumin, *J. clin. Invest. 30*: 1228-37, 1951.
22. Berson, S. A., Yalow, R. S., Schreiber, S. S. and Post, J. Tracer experiments with I^{131} labeled human serum albumin; distribution and degradation studies,

J. clin. Invest. 32:746-68, 1953.

23. Gibson, J. G., II and Evans, W. A., Jr. Clinical studies of the blood volume; the relation of plasma and total blood volume to venous pressure, blood velocity rate, physical measurements, age and sex in ninety normal humans, *J. clin. Invest. 16*:317-28, 1937.
24. Hahn, P. F., Ross, J. F., Bale, W. F., Balfour, W. M. and Whipple, G. H. Red cell and plasma volumes (circulating and total) as determined by radio iron and by dye, *J. exp. Med. 75*:221-32, 1942.
25. Hevesy, G. Köster, K. H., Sørensen, G., Warburg, E. and Zerahn, K. The red corpuscle content of the circulating blood as determined by labelling the erythrocytes with radio-phosphorus, *Acta. med. scand. 116*:361-76, 1944.
26. Gibson, J. G., II, Peacock, W. C., Seligman, A. M. and Sack, T. Circulating red cell volume measured simultaneously by the radioactive iron and dye method, *J. clin. Invest. 25*:838-47, 1946.
27. Meneely, G. R., Wells, E. B. and Hahn, P. F. Application of the radioactive red cell method for determination of blood volume in humans, *Amer. J. Physiol. 148*:531-37, 1947.
28. Reeve, E. B. and Veall, N. A simplified method for the determination of circulating red-cell volume with radioactive phosphorous, *J. Physiol. 108*:12-23, 1949.
29. Nachman, H. M., James, G. W., III, Moore, J. W. and Evans, E. I. A comparative study of red cell volumes in human subjects with radioactive phosphorus tagged red cells and T-1824 dye, *J. clin. Invest. 29*:258-64, 1950.
30. Wasserman, L. R., Yoh, T. and Rashkoff, I. A. Blood volume determination: comparison of T-1824 and P^{32} labeled red cell methods, *J. Lab. clin. Med. 37*: 342-52, 1951.
31. Scott, H. W., Jr., Elliott, S. R., II and Clay, R. C. Blood volume in congenital cyanotic heart disease; simultaneous measurements with Evans blue and radioactive phosphorus, *Bull. Johns Hopkins Hosp. 89*:121-32, 1951.
32. Hirota, K. A new method of measuring the relative volume of the blood corpuscles in the blood, *J. Biophysics 1*:233-57, 1926.
33. Chapin, M. A. and Ross, J. F. Determination of true cell volume by dye dilution, by protein dilution, and with radioactive iron; error of the centrifuge hematocrit, *Amer. J. Physiol. 137*: 447-55, 1942.
34. Mayerson, H. S., Lyons, C., Parson, W., Nieset, R. T. and Trautman, W. V., Jr. Comparison of results of measurement of red blood cell volume by direct and indirect technics, *Amer. J. Physiol. 155*: 232-38, 1948.
35. Vazquez, O. N., Newerly, K., Yalow, R. S. and Berson, S. A. Determination of trapped plasma in the centrifuged erythrocyte volume of normal human blood with radioiodinated (I^{131}) human serum albumin and radiosodium (Na^{24}), *J. Lab. clin. Med. 39*:595-604, 1952.
36. Vazquez, O. N., Newerly, K., Yalow, R. S. and Berson, S. A. Estimation of trapped plasma with I^{131} albumin; critique of methods, *J. appl. Physiol. 6*:437-40, 1954.
37. Berson, S. A., Yalow, R. S., Post, J., Wisham, L. H., Newerly, K. N., Villazon, M. J. and Vazquez, O. N. Distribution and fate of intravenously administered modified human globin and its effect on blood volume; studies utilizing I^{131} tagged globin, *J. clin. Invest. 32*:22-32, 1953.
38. Smith, H. P., Arnold, H. R. and Whipple, G. H. Blood volume studies; comparative values of Welcker, carbon monoxide and dye methods for blood volume determinations; accurate estimation of absolute blood volume, *Amer. J. Physiol. 56*:336-60, 1921.
39. Krogh, A. *The anatomy and physiology of capillaries.* New Haven, Yale Univ. Press, 1922.
40. Fåhraeus, R. The suspension stability of the blood, *Physiol. Rev. 9*:241-71, 1929.
41. Berson, S. A., Yalow, R. S., Azulay, A., Schreiber, S. and Roswit, B. The biological decay curve of P^{32} tagged erythrocytes; application to the study of acute changes in blood volume, *J. clin. Invest. 31*:581-91, 1952.
42. Reeve, E. B. Methods of estimating plasma and total red cell volume, *Nutr.*

Abstr. Rev. 17:811-34, 1948.

43. Mollison, P. L. *Blood transfusion in clinical medicine.* Springfield, Ill., C. C. Thomas, 1951.
44. Gregersen, M. I. Blood volume, *Ann. Rev. Physiol. 13*:397, 1951.
45. Perera, G. A. The effect of significant weight change on predicted plasma volume, *J. clin. Invest. 25*:401-03, 1946.
46. Henschel, A., Mickelsen, O., Taylor, H. L. and Keys, A. Plasma volume and thiocyanate space in famine edema and recovery, *Amer. J. Physiol. 150*:170-80, 1947.
47. Gregersen, M. I. and Nickerson, J. L. Relation of blood volume and cardiac output to body type, *J. appl. Physiol. 3*:329-41, 1950.
48. Forbes, W. H., Dill, D. B. and Hall, F. G. The effect of climate upon the volumes of blood and of tissue fluid in man, *Amer. J. Physiol. 130*:739-46, 1940.
49. Lawrence, J. H., Huff, R. L., Siri, W., Wasserman, L. R. and Hennessy, T. G. A physiological study in the Peruvian Andes, *Acta med. scand. 142*:117-31, 1952.
50. Fryers, G. R. Effect of decreased atmospheric pressure on blood volume of rats, *Amer. J. Physiol. 171*:459-64, 1952.
51. Ebert, R. V. and Stead, E. A., Jr. Demonstration that in normal man no reserves of blood are mobilized by exercise, epinephrine, and hemorrhage, *Amer. J. med. Sci. 201*:655-64, 1941.
52. Kaltreider, N. L. and Meneely, G. R. The effect of exercise on the volume of the blood, *J. clin. Invest. 19*:627-34, 1940.
53. Nylin, G. The effect of heavy muscular work on the volume of circulating red corpuscles in man, *Amer. J. Physiol. 149*:180-84, 1947.
54. McLennan, C. E. and Thouin, L. G. Blood volume in pregnancy, *Amer. J. Obstet. Gynec. 55*:189-200, 1948.
55. Thompson, W. O., Thompson, P. K. and Dailey, M. E. The effect of posture upon the composition and volume of the blood in man, *J. clin. Invest. 5*: 573-604, 1928.
56. Perera, G. A. and Berliner, R. W. The relation of postural hemodilution to paroxysmal dyspnea, *J. clin. Invest. 22*: 25-28, 1943.
57. McMichael, J. and McGibbon, J. P. Postural changes in lung volume, *Clin. Sci. 4*:175-83, 1939.
58. Sjöstrand, T. Volume and distribution of blood and their significance in regulating circulation, *Physiol. Rev. 33*:202-28, 1953.
59. Altschule, M. D., Zamchek, N. and Iglauer, A. The lung volume and its subdivisions in the upright and recumbent positions in patients with congestive failure. Pulmonary factors in the genesis of orthopnea, *J. clin. Invest. 22*: 805-12, 1943.
60. Gibson, J. G., II, Harris, A. W. and Swigert, V. W. Clinical studies of the blood volume; macrocytic and hypochromic anemias due to chronic blood loss, hemoptysis and miscellaneous causes, and polycythemia vera, *J. clin. Invest. 18*:621-32, 1939.
61. Berlin, N. I., Lawrence, J. H. and Gartland, J. Blood volume in polycythemia as determined by P^{32} labeled red blood cells, *Amer. J. Med. 9*:747-51, 1950.
62. Berson, S. A. and Yalow, R. S. Unpublished observations.
63. Gibson, J. G., II. Clinical studies of the blood volume; changes in blood volume in pernicious anemia in relation to the hematopoietic response to intramuscular liver extract therapy, *J. clin. Invest. 18*:401-14, 1939.
64. Ebert, R. V., Stead, E. A., Jr. and Gibson, J. G., II. Response of normal subjects to acute blood loss with special reference to the mechanism of restoration of blood volume, *Arch. intern. Med. 68*:578-90, 1941.
65. Wallace, J. and Sharpey-Schafer, E. P. Blood changes following controlled hemorrhage in man, *Lancet 2*:393-95, 1941.
66. Noble, L. P. and Gregersen, M. I. Blood volume in clinical shock; extent and cause of blood volume reduction in traumatic, hemorrhage, and burn shock, *J. clin. Invest. 26*:172-83, 1946.
67. Grant, R. T. and Reeve, E. B. G. *Observations on the general effects of injury in man.* Medical research council.

Special report series, London, H.M.S.O., 1951, No. 277.

68. Fine, J. and Seligman, A. M. Traumatic shock; a study of the problem of the "lost plasma" in hemorrhagic shock by the use of radioactive plasma protein, *J. clin. Invest. 22*:285-303, 1943.
69. Cope, O. and Moore, F. D. A study of capillary permeability in experimental burns and burn shock using radioactive dyes in blood and lymph, *J. clin. Invest. 23*:241-57, 1944.
70. Fox, C. L., Jr. and Keston, A. S. The mechanism of shock from burns and trauma traced with radiosodium, *Surg. Gynec. Obstet. 80*:561-67, 1945.
71. Fox, C. L., Jr. Oral sodium lactate in the treatment of burn shock, *J. Amer. med. Assoc. 124*:207-12, 1944.
72. Millican, R. C., Tabor, H. and Rosenthal, S. M. Traumatic shock in mice; comparison of survival rates following therapy, *Amer. J. Physiol. 170*:179-86, 1952.
73. Hartman, F. W. and Behrmann, V. G. The present status of plasma extenders, *J. Amer. med. Assoc. 152*:1116-20, 1953.
74. Berson, S. A. and Yalow, R. S. The spaces of distribution of tagged erythrocytes and I^{131} labeled human serum albumin and of Na^{24} and Br^{82}, *Clin. Chemist 5*:41, 1953.
75. Lyon, R. P., Stanton, J. R., Freis, E. D. and Smithwick, R. H. Blood and "available fluid" (thiocyanate) volume studies in surgical patients; normal patterns of response of the blood volume, available fluid, protein, chloride and hematocrit in the postoperative surgical patient, *Surg. Gynec. Obstet. 89*:9-19, 1949.
76. Winkler, A. W., Danowski, T. S. and Elkinton, J. R. The role of colloid and of saline in the treatment of shock, *J. clin. Invest. 25*:220-25, 1946.
77. Strumia, M. M., Chornock, F. W., Blake, A. D. and Kerr, W. G. The use of a "modified globin" from human erythrocytes as a plasma substitute: preliminary report, *Amer. J. med. Sci. 209*:436-42, 1945.
78. Heyl, J. T., Gibson, J. G., II and Janeway, C. A. Studies on the plasma proteins; the effect of concentrated solution of human and bovine serum albumin on blood volume after acute blood loss in man, *J. clin. Invest. 22*: 763-73, 1943.
79. Scatchard, G., Strong, L. E., Hughes, W. L., Jr., Ashworth, J. N. and Sparrow, A. H. Chemical, clinical and immunological studies on the products of human plasma fractionation; the properties of human serum albumin of low salt content, *J. clin. Invest. 24*:671-79, 1945.
80. Fletcher, A. G., Jr., Hardy, J. D., Riegel, C. and Koop, L. E. Gelatin as a plasma substitute; the effects of intravenous infusion of gelatin on cardiac output and other aspects of the circulation of normal persons, of chronically ill patients and of normal volunteers subjected to large hemorrhage, *J. clin. Invest. 24*:405-15, 1945.
81. Pulaski, E. J. Clinical status of plasma substitutes, *Chem. Engng. News 30*: 2187-89, 1952.
82. Barker, H. G., Elder, J. D., Walker, J. M. and Vars, H. M. The retention of certain plasma volume expanders within the circulation of human subjects following a 1,000 cubic centimeter hemorrhage, *Surgery 32*:299-303, 1952.
83. Hammarsten, J. F., Heller, B. I. and Ebert, R. V. The effects of dextran in normovolemic and oligemic subjects, *J. clin. Invest. 32*:340-44, 1953.

83a. Bryan, G. C. and Scudder, J. Dextran and pneumococcus polysaccharide cross reactivity in skin tests and serum precipitin tests, in Shock syndrome, *Ann. N. Y. Acad. Sci. 55*:477-78, 1952.

84. Gibson, J. G., II and Evans, W. A., Jr. Clinical studies in blood volume; changes in blood volume, venous pressure and blood velocity rate in congestive heart failure, *J. clin. Invest. 16*: 851-58, 1937.
85. Seymour, W. B., Pritchard, W. H., Langley, L. P. and Hayman, J. M., Jr. Cardiac output, blood and interstitial fluid volumes, total circulating serum protein, and kidney function during cardiac failure and after improvement, *J. clin. Invest. 21*:229-40, 1942.
86. Meneely, G. R. and Kaltreider, N. L.

A study of the volume of the blood in congestive heart failure. Relation to other measurements in fifteen patients, *J. clin. Invest. 22*:521-30, 1943.

87. Ross, J. F., Chodos, R. B., Baker, W. H. and Freis, E. D. The blood volume in congestive heart failure, *Trans. Assoc. Amer. Phycns. 65*:75-86, 1952.
88. Prentice, T. C., Berlin, N. I., Hyde, G. M., Parsons, R. J., Lawrence, J. H. and Port, S. Total red cell volume, plasma volume and sodium space in congestive heart failure, *J. clin. Invest. 30*:147-82, 1951.
89. Eisenberg, S. The effect of congestive heart failure on the blood volume as determined by radioactive chromium tagged red cells, *Clin. Res. Proc.* 1953, Abst. 31.
90. Schreiber, S. S., Bauman, A., Yalow, R. S. and Berson, S. A. Blood volume alterations in congestive heart failure, *J. clin. Invest. 33*:578-86, 1954.
91. Fryers, G. R. and Berlin, N. I. Mean red cell life of rats exposed to reduced barometric pressure, *Amer. J. Physiol. 171*:465-70, 1952.
92. Hiller, G. I., Huffman, E. R. and Levey, S. Studies in cirrhosis of the liver; relationship between plasma volumes, plasma protein concentrations and total circulating proteins, *J. clin. Invest. 28*:322-30, 1949.
93. Bateman, J. C., Shorr, H. M. and Elgvin, T. Hypervolemic anemia in cirrhosis, *J. clin. Invest. 28*:539-47, 1949.
94. Harris, A. W. and Gibson, J. G., II. Clinical studies of the blood volume; changes in blood volume in Bright's disease with or without edema, renal insufficiency or congestive heart failure, and in hypertension, *J. clin. Invest. 18*: 527-36, 1939.
95. Blalock, A. Mechanism and treatment of experimental shock; shock following hemorrhage, *Arch. Surg. 15*:762-98, 1927.
96. Remington, J. W., Remington, R. E. and Caddell, H. H. Production of circulatory failure by electrolyte depletion, *Amer. J. Physiol. 170*:564-73, 1952.
97. Zweifach, B. W., Lee, R. E., Hyman, C. and Chambers, R. Omental circulation in morphinized dogs subjected to graded hemorrhage, *Ann. Surg. 120*: 232-50, 1944.
98. Shorr, E. The role of hepatorenal vasoactive factors in experimental shock, in *Symposium on Shock* at Army Medical Service Graduate School, Washington, D. C., May 7-9, 1951, IV-1 to IV-33.
99. Page, I. H. Control of the caliber and reactivity of the blood vessels in shock, in *Symposium on Shock* at Army Medical Service Graduate School, Washington, D. C., May 7-9, 1951, X-1 to X-15.
100. Cournand, A., Riley, R. L., Bradley, S. E., Breed, E. S., Noble, R. P., Lauson, H. D., Gregersen, M. I. and Richards, D. W. Studies of the circulation in clinical shock, *Surgery 13*:964-95, 1943.
101. Warren, J. V., Brannon, E. S., Stead, E. A., Jr. and Merrill, A. J. The effect of vivisection and the pooling of blood in the extremities on the atrial pressure and cardiac output in normal subjects with observations on acute circulatory collapse in 3 instances, *J. clin. Invest. 24*:337-44, 1945.
102. Madden, S. C. and Whipple, G. H. Plasma proteins: their source, production and utilization, *Physiol. Rev. 20*: 194-217, 1940.
103. Yeomans, A., Porter, E. R. and Swank, R. L. Observations on certain manifestations of circulatory congestion produced in dogs by rapid infusion, *J. clin. Invest. 22*:33-45, 1943.
104. Starling, E. H. *The fluids of the body.* Chicago, Ill., W. T. Keener & Co., 1909.
105. Peters, J. P. The problem of cardiac edema, *Amer. J. Med. 12*:66-76, 1952.
106. Fahr, G. and Ershler, I. Studies of the factors concerned in edema formation; the hydrostatic pressure in the capillaries during edema formation in right heart failure, *Ann. intern. Med. 15*: 798-810, 1941.
107. Landis, E. M., Brown, E., Fauteux, M. and Wise, C. Central venous pressure in relation to cardiac "competence," blood volume and exercise, *J. clin. Invest. 25*:237-55, 1946.
108. Smirk, F. H. Observations on the

causes of edema in congestive heart failure, *Clin. Sci. 2*:317-35, 1936.

109. Stead, E. A., Jr. and Warren, J. V. The protein content of the extracellular fluid in normal subjects after venous congestion and in patients with cardiac failure, anoxemia, and fever. *J. clin. Invest. 23*:283-87, 1944.
110. Starr, I., Jeffers, W. A. and Meade, R. H., Jr. The absence of conspicuous increments of venous pressure after severe damage to the right ventricle of the dog, with a discussion of the relation between clinical congestive failure and heart disease, *Amer. Heart J. 26*:291-301, 1943.
111. Warren, J. V. and Stead, E. A., Jr. Fluid dynamics in chronic congestive heart failure, *Arch. intern. Med. 73*: 138-47, 1944.
112. Starr, I. Role of the "static blood pressure" in abnormal increments of venous pressure, especially in heart failure; clinical and experimental studies, *Amer. J. med. Sci. 199*:40-55, 1940.
113. Merrill, A. J. Edema and decreased renal blood flow in patients with chronic congestive heart failure: evidence of "forward failure" as the primary cause of edema, *J. clin. Invest. 25*:389-400, 1946.
114. Kaltreider, N. L. and Meneely, G. R. The effect of exercise on the volume of the blood, *J. clin. Invest. 19*:627-34, 1940.
115. Roos, A. and Smith, J. R. Production of experimental heart failure in dogs with intact circulation, *Amer. J. Physiol. 153*:558-66, 1948.
116. Reichsman, F. and Grant, H. Some observations on the pathogenesis of edema in cardiac failure, *Amer. Heart J. 32*:438-42, 1946.
117. Blake, W. D., Wégria, R., Keating, R. P. and Ward, H. P. The effect of increased renal venous pressure on renal function, *Amer. J. Physiol. 157*:1-13, 1949.
118. Landis, E. M. and Gibbon, J. H., II. The effects of temperature and of tissue pressure on the movement of fluid through the human capillary wall, *J. clin. Invest. 12*:105-38, 1933.
119. Warren, J. V., Elkin, D. C. and Nickerson, J. L. The blood volume in patients with arteriovenous fistulas, *J. clin. Invest. 30*:220-26, 1951.
120. Elkin, D. C. and Warren, J. V. Arteriovenous fistulas; their effect on the circulation, *J. Amer. med. Assoc. 134*: 1524-28, 1947.
121. Blumgart, H. L. and Freedberg, A. S. The heart and the thyroid: with particular reference to I^{131} treatment of heart disease, *Circulation 6*:222-37, 1952.
122. Myant, N. B., Pochin, E. E. and Goldie, E. A. G. The plasma iodine clearance rate of the human thyroid, *Clin. Sci. 8*:109-33, 1949.
123. Berson, S. A., Yalow, R. S., Sorrentino, J. and Roswit, B. The determination of thyroidal and renal plasma I^{131} clearance rates as a routine diagnostic test of thyroid dysfunction, *J. clin. Invest. 31*:141-58, 1952.
124. Wégria, R., Frank, C. W., Wang, H. H. and Miller R. Effect of arteriovenous fistula on the circulation (abstract), *J. clin. Invest. 31*:670, 1952.
125. Sieker, H. O., Gauer, O. H. and Henry, J. P. The effect of negative pressure breathing on renal function (abstract), *J. clin. Invest. 31*:662, 1952.
126. Viar, W. N., Oliver, B. B., Eisenberg, S., Lombardo, T. A., Willis, K. and Harrison, T. R. The effect of posture and of compression of the neck on excretion of electrolytes and glomerular filtration, *Circulation 3*:105-15, 1951.
127.* Berson, S. A., Yalow, R. S., Schreiber, S., Baumann, A. and Rothschild, M. Unpublished data.
128.* Berlin, N. I., Lawrence, J. H. and Gartland, J. The blood volume in chronic leukemia as determined by P^{32} labeled red blood cells, *J. Lab. clin. Med. 36*:435-39, 1950.

* Cited in Table I.

THE FAILING HEART

*Transcription of a Panel Meeting on Therapeutics**

CHARLES E. KOSSMANN . . . Moderator

Associate Professor of Medicine, New York University College of Medicine

Panel Members

ROBERT C. BATTERMAN

Assistant Professor of Medicine, New York Medical College

CARY EGGLESTON

Associate Professor of Clinical Medicine, Cornell University Medical College

LUDWIG EICHNA

Associate Professor of Medicine, New York University College of Medicine

CHARLES K. FRIEDBERG

Assistant Clinical Professor of Medicine, College of Physicians and Surgeons, Columbia University

* Presented in the Monthly Panel Meeting Series, March 6, 1953, at The New York Academy of Medicine.

MODERATOR CHARLES E. KOSSMANN: Ladies and Gentlemen, it is my privilege to welcome you to this fifth of the monthly panel conferences on therapeutics arranged for you by The New York Academy of Medicine. As you know, today the subject is "The Failing Heart."

I need hardly say to this group of practicing physicians anything about the magnitude of this problem which I think you will agree is becoming greater as the population ages. It is also becoming greater because it appears that the man or woman with the failing heart lives a very much longer time than he or she formerly did. I think we can ascribe this to two important changes that have been made in the last decade or so in the management of the failing heart. I would say that those two important changes concern the advent of non-toxic mercurial diuretics and the use of the sodium restricted diet.

This panel is purely one on therapeutics. There will be an usher going up and down the aisles with paper for any of you who want to submit a question. The whole purpose of this panel is to answer your questions on the management of the failing heart. This panel has not met before this moment. We have no pre-arranged program. There will be no introductory remarks with two exceptions. First, I would like to take a few moments to introduce to you the members of your panel.

From the customary left to right, we have Dr. Cary Eggleston, Associate Professor of Clinical Medicine, Cornell University Medical College. I think all of you know Dr. Eggleston. Perhaps not all of you know that the first paper on digitalis dosage written by him was in 1915, a considerable period of time, perhaps, before most of us had even thought of entering medical school. He is the elder statesman of this panel and will keep the younger members in check in case they get a little wild.

The next man is Dr. Charles K. Friedberg, Assistant Clinical Professor of Medicine, College of Physicians and Surgeons, Columbia University. You all know Dr. Friedberg from the excellent book that has appeared in recent years under his authorship.

The next man is Dr. Robert C. Batterman, Assistant Professor of Medicine, New York Medical College. Dr. Batterman has devoted a great part of his professional life to the study of the mercurial diuretics and digitalis glycosides and he was also instrumental in introducing to clinical medicine a very important drug in the management of the patient with a failing heart, namely, meperidine hydrochloride (Demerol).

The last man is Dr. Ludwig Eichna, Associate Professor of Medicine,

New York University College of Medicine. Dr. Eichna is on the panel because of his interest in the hemodynamics of congestive heart failure. We shall call on Dr. Eichna for several aspects of management of the failing heart that may relate to its hemodynamics. Those are the first of the introductory remarks that I said would be made.

The second is this: I think that before we go into a discussion of the failing heart we ought to be pretty clear in our own minds what we mean by the failing heart. I think all of us have a pretty good general conception of what that is, but perhaps before we go into therapeutics, it would be well just for the record to be sure what we mean by the failing heart and so for a definition of the failing heart I am going to call on Dr. Eichna.

DR. LUDWIG EICHNA: My first comment is, oh, dear! I think the panel could easily get bogged down in a definition of the failing heart without any "ifs," "ands" or "buts" and with the realization of the tremendous assumptions made, suppose I give the following definition: The failing heart is one in which, for some as yet unknown reason, the chemical energy which is available to the myocardium is not properly transmitted into mechanical energy with the result that the myocardium cannot perform the work of propelling a sufficient amount of blood for the needs of the total bodily metabolism. As a consequence of this failure of blood supply in the required amount to all of the organs there results the commonly recognized syndrome of venous congestion, whether it be in back of the right ventricle to give congested veins, a large liver, edema or whether the venous congestion be back of the left ventricle to give dyspnea, orthopnea and rales. It is on these peripheral manifestations that we base our diagnosis of the more serious primary defect. This is the best I can do.

MODERATOR KOSSMANN: Thank you, Dr. Eichna.

Would you like to emphasize that there are some situations that could easily be confused with congestive heart failure?

DR. EICHNA: This, Dr. Kossmann, is a problem which is interesting us much at the moment. I mentioned that the failing myocardium gave rise to a series of peripheral manifestations and that on the basis of these peripheral manifestations we come to a conclusion as to what is wrong with the myocardium. Now if you will think for a moment, these peripheral manifestations are non-specific. They are simply the manifestations of venous congestion.

Just one example of where venous congestion may occur without a failing heart. If you have an anuric patient with lower nephron nephrosis and that patient is overloaded with intravenous fluids, the circulation becomes congested, he develops engorged neck veins and a large liver. He becomes edematous. Rales are present. He may develop pulmonary edema and he may die. This is not due, in my mind, to a failure of the heart. This is venous congestion induced artificially by overloading the circulation. This, Dr. Kossmann, I think is one type of venous congestion which is non-cardiac, which probably cannot be treated in the same manner as the same symptoms and syndrome developing from failure of the myocardium itself.

MODERATOR KOSSMANN: Thank you, Dr. Eichna.

I think perhaps that starts us off, at least in the right direction. *Now I would like to say I have a question here that is related, as a matter of fact, to this whole problem and it is: Can a normal heart be made to fail, for example, by prolonged, high rate tachycardia?*

Would you like to answer that, Dr. Eggleston?

DR. CARY EGGLESTON: Dr. Kossmann, I think probably a normal heart can be made to fail as a result of a prolonged high degree of tachycardia. On the other hand, one can retort to that opinion by pointing out that the tachycardia's occurrence is an indication of some disturbance in the heart or the heart's mechanism, and hence we may not be judging right to classify such a heart as a normal heart.

MODERATOR KOSSMANN: *Are there any other members of the panel who would like to comment on this particular problem?*

DR. ROBERT C. BATTERMAN: I think the question presented, whether a normal heart can develop heart failure as the result of a tachycardia, is one dependent upon time. The behavior of a normal heart that has been functioning well before it is given too much work to do as in the case of stress, whether it is a tachycardia from an irritable focus or tachycardia on the basis of excessive exertion, is dependent upon how long that stress is going to continue. As a rule in the normal individual with a short duration of that tachycardia, heart failure may not occur in the form we usually recognize as heart failure in terms of pulmonary edema, enlargement of the liver or peripheral edema. The patient may manifest dyspnea or a sense of suffocation but not real heart failure in the term of a complete break of the heart reserve. We all know that if a tachycardia should persist for many years, then as a compensatory mechanism for the tachy-

cardia the heart will hypertrophy and then at some time the patient will subsequently go into heart failure. In a normal individual a tachycardia of short duration will not result in heart failure.

MODERATOR KOSSMANN: Dr. Friedberg.

DR. CHARLES K. FRIEDBERG: I should like to make two comments about the discussion thus far. In the first place, I think it is important to emphasize that, as a rule, even with severe tachycardias, the normal heart does not fail, does not produce the series of symptoms that we call heart failure. In other words, it is valuable for differential diagnosis to distinguish between the heart which fails as the result of a tachycardia with a ventricular rate that exceeds 180 per minute and the heart, which, in spite of such tachycardia, does not fail. In short, then, the normal heart may begin to show symptoms of failure with tachycardia causing extreme strains, but this is the exception rather than the rule. This leads to the second point, namely, that many of the symptoms which we regard as heart failure are evidences of a load beyond the capacity of that heart, but even the normal heart has a reserve which though great is limited. Thus, for example, normally we can run a certain distance or we can walk a certain distance, or go up hill without dyspnea, usually a primary symptom of heart failure. That is true of the normal person. One can go so far but with a little more speed or a little more exertion even the normal individual has dyspnea. Yet we do not say he has heart failure at that moment. Similarly, but to a lesser extent, we can say that edema, as denoted by weight gain, can be induced if the normal person will take, for example, 25 grams of sodium chloride daily for more than three or four days. It is difficult to do but you could waterlog the patient and produce the clinical manifestations of heart failure. I don't think we can properly say that the patient had heart failure if he experienced dyspnea with unusual exertion or edema with enormous sodium intake. Therefore when we consider whether the normal heart can fail we really ought to say, does the normal heart fail with strains which are within the range of what we regard as normal activity?

DR. EGGLESTON: What would your answer to that question be if it were put to you?

DR. FRIEDBERG: You mean by a lawyer?

DR. EGGLESTON: By a medical man.

DR. FRIEDBERG: Yes or no, I would have to make the reply with a reservation. I agree with you that the normal heart may fail in the sense

that a patient having a marked tachycardia, which is especially persistent, begins to develop dyspnea and may develop rales at the bases of the lungs. I merely wanted to stress for the audience that it is more common that the normal heart tolerates tachycardia well, that the abnormal heart with a lesser reserve will more readily and more frequently develop the clinical syndrome that we call congestive heart failure.

MODERATOR KOSSMANN: While we are on the subject of tachycardias, I think everyone is aware that the patient with organic heart disease can develop tachycardia arising from a variety of foci. Let us assume that the patient has auricular tachycardia occurring in the course of some disease which might eventually go on to heart failure. *What would be the treatment of choice in the patient who has developed congestive heart failure as a result of auricular tachycardia, Dr. Batterman?*

DR. BATTERMAN: I think the choice of any therapeutic measure under such circumstances is dependent upon the underlying heart disease and not the tachycardia. If the patient has a myocardial infarction accompanied by auricular tachycardia, the choice of a certain drug might be quite different from the case where there was long-standing rheumatic heart disease and the occurrence of auricular tachycardia. But taking it as a group now, without knowing the etiology of the underlying heart disease, the drug of choice would be a digitalis preparation. Assuming that simple conservative measures such as carotid pressure, ocular pressure, induced vomiting, or sedation have not controlled the tachycardia, and the patient is in heart failure, then digitalization is indicated. Again we have to assume that the patient has not had any digitalis in the recent past or within a very reasonable period before the onset of the tachycardia.

MODERATOR KOSSMANN: *Dr. Batterman, is there any particular way you would prefer to give the digitalis in such a patient?*

DR. BATTERMAN: That again depends upon the severity of the signs and symptoms of the heart failure at the time the tachycardia is noted. If we are courageous enough not to treat a group of patients with a paroxysmal tachycardia, we note that the tachycardia sort of tires itself out the longer it persists and drugs which are less effective at the onset of the tachycardia are more effective later on. For example, if one were to use acetyl beta methyl choline, it is less effective immediately after the onset of the paroxysmal tachycardia than after the tachycardia has been present for several hours. If the patient is in serious, critical condition,

then the parenteral use of a glycoside is indicated. If the patient is in good condition, as you can judge from the clinical point of view—purely a rough guide—then oral digitalization would be preferable. The drug that I would try to avoid is quinidine because if quinidine does not work in these cases, then you may prevent the action of other therapeutic measures, because quinidine may be depressant on some of the pharmacologic actions of digitalis or acetyl beta methyl choline.

MODERATOR KOSSMANN: In myocardial infarction we occasionally see ventricular tachycardia. We also see ventricular tachycardia in the case of Stokes-Adams' seizures. There has recently been made available to the clinician a very potent and useful procaine amide, Pronestyl being the trade name. *Dr. Eichna, would you like to say something about the use of Pronestyl in the treatment of ventricular tachycardia, first in the course of myocardial infarction and second, in the case of complete heart block with Adams-Stokes' seizures?*

DR. EICHNA: The use of the drugs under the two conditions is entirely different. In a ventricular tachycardia with myocardial infarction there is every reason to attempt to suppress that tachycardia, the danger being of course ventricular flutter or ventricular fibrillation and death. Under such circumstances I would not hesitate to use Pronestyl, or if you wish, quinidine. I think experience has shown that ventricular tachycardia in the presence of complete A-V dissociation is an entirely different picture,—that here Pronestyl instead of preventing the tachycardia tends to potentiate it. Several papers in the literature during the past fall (1952) have indicated this and in our experience the same thing has occurred. Patients who have had ventricular tachycardia with Adams-Stokes' attacks on the basis of complete dissociation, and who were given even small doses of Pronestyl, have shown ventricular tachycardias, with in one instance an unfavorable outcome.

As to dose, I would give Pronestyl orally unless there is a specific reason to give it intravenously. If the patient with myocardial infarction is in shock, if it appears as though death is imminent, then I think, one might in spite of the lowered blood pressure give the drug intravenously at the rate of approximately 100 mg. per minute, not faster than 100 mg. per minute, to a total not to exceed one gram. If the patient can take the drug by mouth, I would give the same dosage by mouth because it is readily absorbed.

MODERATOR KOSSMANN: *Dr. Friedberg, sometimes in his enthusiasm*

the physician induces ventricular tachycardia with digitalis. What about the use of procaine amide in that situation?

DR. FRIEDBERG: I think the indication is just as good for procaine amide in ventricular tachycardia due to digitalis as in the type that Dr. Eichna discussed.

Of course, in all forms of therapy I like to attack the cause if that is possible. That means that one of the dangers, in cases of ventricular tachycardia due to digitalis intoxication, is the failure to recognize that the tachycardia is actually due to the digitalis and to misinterpret the tachycardia as an indication for further digitalization. Therefore the first point to stress is that one must recognize the etiology and discontinue the digitalis. Having done that one has three major drugs that may be used, and the one which I will give first choice is Pronestyl or procaine amide. Another is to consider the advisability of the administration of potassium salts since a diminution of myocardial potassium is concerned in the heightened irritability of the myocardium to digitalis. Finally, although there has been some difference of opinion about it, ventricular tachycardia due to digitalis may be controlled by quinidine. Such cases have been reported and I have observed this myself. There has been some hesitation by others to use quinidine in patients who have had ventricular tachycardia caused by digitalis.

MODERATOR KOSSMANN: Thank you, Dr. Friedberg.

Ladies and Gentlemen, your questions are lagging a little bit. The usher will come up and down the aisle; please give your questions to him. You are here to stump the experts by your questions, by your problems.

Dr. Eggleston, I have a question for you, a sort of general one, but perhaps it can start the ball rolling on digitalis. Which digitalis is the one of choice in the treatment of the failing heart?

DR. EGGLESTON: That, of course, is a matter of personal opinion and experience. My own experience leads me to give my first choice to crystalline digitoxin. I realize that that choice has certain drawbacks. It is not possible to induce digitalization where such is necessary with great rapidity by the administration of digitoxin, even when it is given intravenously. There is a certain lag period that we must allow to elapse. If the condition be sufficiently urgent then I would use one of the lanatosides. They act much more rapidly upon the heart than digitoxin, or I would use ouabain, the crystalline strophanthin G intravenously.

MODERATOR KOSSMANN: Whenever you get into a discussion of

which digitalis preparation is best for the treatment of the failing heart you are bound to have differences of opinion, so I think I am going to put this same question to all members of the panel. *Dr. Friedberg, would you like to say a word or two about what you consider the preparation of choice for the treatment of the failing heart?*

DR. FRIEDBERG: I often think of the digitalis preparations as I do of anesthetics, namely, that they are all useful. They can all be used and I prefer to use that with which I have acquired the greatest familiarity. Many of my patients who were originally digitalized by means of whole leaf are still continued on the whole leaf. On theoretical grounds, I think it is preferable today to use one of the digitalis glycosides and I think they will replace the whole leaf more and more because of certain advantages of standardization which I think will continue to improve. At the present time I use Digoxin, one of the lanatoside preparations, more frequently than any of the others in new patients. As I said, I think the leaf is still being used by most of my old patients. In addition I have been using gitalin, the one glycoside of digitalis purpurea not present in digitalis lanata. Digitoxin and gitoxin are two alkaloids present in both purpurea and lanata digitalis preparations. Gitalin is an interesting preparation because it is said that the range between the therapeutic and toxic doses is much greater than that of the other glycosides. I myself have always had a skepticism about such claims. But I find it an effective preparation and one which has not given me any difficulty.

MODERATOR KOSSMANN: *Dr. Friedberg, the man who made that claim is on your left and will be the next speaker.*

DR. BATTERMAN: The choice of a digitalis preparation is dependent upon many factors other than the glycosides or preparation itself. The problem is actually twofold, the initial digitalization and the maintenance of the restored compensated state. The initial digitalization is also dependent upon the emergency that arises and the rapidity with which you desire digitalization. For rapid digitalization you would prefer an intravenous or parenteral glycoside, preferably Lanatoside C. If you give it orally, then you must consider many factors. Again we go back to the type of heart disease that is present and whether or not that patient's heart has deteriorated to such a point that it has lost its ability to respond to a digitalis preparation. The use of the preparations of digitalis is similar to the use of any other drug in the field of medicine. There is no way of looking at the patient and predicting in advance what the opti-

mum dosage shall be. In a way you have to titrate your patient with decreasing doses taking into account the peak of level of each administered dose and the dissipation of effect of that particular dose. In other words, you cumulate a certain action depending upon the doses that you administer. You cannot predict what that optimum dose will be in advance, the point being that in the average patient you can achieve digitalization or a therapeutic effect before you achieve toxicity. If you want to consider averages, with most digitalis preparations, two-thirds of the toxic dose represent the therapeutic dose. We say the difference between the therapeutic dose and toxic dose is the therapeutic range but it is impossible to predict what that range will be in any particular patient. You may find that your patient will become toxic before a therapeutic effect has developed and the patient cannot respond to digitalization. That occurs in patients with myocardial infarcts or advanced fibrosis or patients with rheumatic heart disease that have advanced fibrosis. If you suspect that such a condition exists one would not use a preparation where the dissipation factor is prolonged. If toxicity should occur the toxic manifestations may persist for several days or weeks. You would prefer to use one that is rapidly dissipated like Digoxin. If, however, you take the average patient and the therapeutic range is only one-third, you have a better chance of obtaining the therapeutic dose without toxicity. It should be emphasized that no patient with heart failure should be treated to the point of toxicity. We would like to stop the repeated administration of the dose when the compensation occurs. In order to help you obtain a better range, we recommend gitalin, because the therapeutic dose is one-third of the toxic dose in the majority of the patients. That has a certain advantage in some of your patients, particularly in the ambulatory maintenance state. You may find that many patients cannot tolerate any equivalent dose of digitoxin, digitalis leaf or Digoxin. They become toxic without restoration of maintenance. They have abolished the therapeutic range. However, if you use gitalin in many of these patients you can now obtain a therapeutic effect because they will not become toxic with equivalent doses. For the usual patient we prefer gitalin, since it has a greater range. It does not persist in its toxicity as long as digitalis leaf, squill or digitoxin. However, in patients with advanced heart disease where you are afraid of irritability, then Digoxin is the drug of choice.

MODERATOR KOSSMANN: *Dr. Batterman, just for our information,*

would you tell us what the daily average maintenance dose of gitalin is?

DR. BATTERMAN: Half a milligram of gitalin is equivalent to one-tenth of a gram of leaf or one-tenth of a milligram of digitoxin, within certain biological variations. This may fluctuate plus or minus a quarter of a milligram, but that dose has the greatest predictability of producing maintenance and least likelihood of toxicity.

MODERATOR KOSSMANN: *Dr. Eichna, I wish you would continue this discussion along the line of this question: With purified glycosides readily available (and more expensive, I might say) does digitalis leaf still have a place in the treatment of the failing heart?*

DR. EICHNA: The answer is yes. To amplify, I think the problem should be considered from two points of view. Do you need digitalis in an emergency or do you have time and may you give a digitalis preparation more leisurely? Answering the second point first, do you have time, as far as I am concerned it is a toss-up whether you take digitalis leaf, Digoxin, digitoxin, gitalin or any of the other preparations. It seems to me that they all work about equally well. There is one proviso and I think Dr. Eggleston brought that out: Know your drug! If you have learned to know one preparation and how to use it, it will behave well for you. Of course, when you are faced with an emergency, then you are limited and most of the time I think that brings you down to Digoxin and ouabain. Ouabain is the fastest acting glycoside we have. It will produce its effect in about fifteen minutes. Digoxin will act almost as rapidly, in about thirty minutes. If you have a patient with rheumatic heart disease who is in labor and who has not been digitalized and is going into congestive failure or one who presents a surgical emergency, then these two preparations are very helpful. About a half milligram of ouabain should be given intravenously for an initial dose. If there is no effect, you may give another 0.2 mg. after half an hour. The dosage of Digoxin is usually from 0.5 to 1.0 mg. on the first dose. I recommend a half milligram rather than one, and repeat again after half an hour but do not give more than about 1.5 mg. within the first hour. In my own way of looking at it, if I get into trouble with any of the glycosides or the other preparations I almost always wipe the slate clean and go back to good old digitalis leaf until I get the patient straightened out. I must say that in spite of theoretical considerations and the gravimetric, instead of animal assay, digitalis leaf still has not failed.

As I have been a little bit against digitoxin because of the persistence

of toxic effects when they do occur, particularly the arrhythmias,—I would like to ask Dr. Eggleston what is your experience along that line?

DR. EGGLESTON: I am very glad you brought that up because I have been asked that same question on many occasions. I don't think that I have any particular difficulty with that problem. It seems to me that the dose for that agent in the majority of patients is pretty well established and if you do not exceed or fall too far below that dose you will obtain satisfactory digitalization in a reasonable period of time. That dose is somewhere in the neighborhood of 1.5 mg. for a patient. That is crystalline digitoxin.

As to the persistence of action, which may be and is considered by many to be a disadvantage, I do not see it that way. I think if we approach our therapeutic level of digitalization a bit cautiously toward the end of our administration we can avoid most of the toxic effects. I don't mean to say that that is applicable in all patients because it certainly is not. There are some patients who are supersensitive to all of the digitalis bodies, or particularly to some one or more of the entire range and one must then try out the different ones.

Years ago when we were investigating digitalis bodies, we found that they were mutually synergistic when introduced into the blood stream of the experimental animal. Fifty per cent of the toxic dose of any one plus 50 per cent of the toxic dose of any other equalled 100 per cent of the toxic dose of either of those preparations. I fail to see why we cannot therefore adjust our use of any of these digitalis preparations, glycosides, to meet the needs at hand and I have tried for many years to preach that upon every occasion, the problem is to meet the patient's needs under the existing conditions and I do not care whether you do that with one glycoside or another, or whether you do it with the whole leaf. The difficulty with the whole leaf is the amount of residual inactive material that is there and that cannot be estimated, plus the fact that the assay must be biological which we know is definitely less accurate than when we are attempting to use a dose based upon a crystalline preparation or a purified glycoside.

MODERATOR KOSSMANN: *Dr. Friedberg.*

DR. FRIEDBERG: I agree with everything Dr. Eggleston has said except I think that we should not infer from that that we are all able to handle the drug as well as he can. As a matter of practical experience I have found that since digitoxin has been available, the incidence of toxicity

has been, to my mind, appalling. I must assume, therefore, not that the drug cannot be given by the expert without this high degree of toxicity, but that there must be something in the drug or the dosage or our method of handling it at the present time which makes for a high incidence of toxicity and I think we ought to accept the fact as it is. I think one reason for it is that the original recommendation of the average of about 1.2 mg. for digitalization and 0.2 mg. daily for maintenance was faulty. This dosage may have been satisfactory for the digitalization, although I think for many people it was inadequate, but for maintenance I am sure it is much too high. In my experience most patients when digitalized can be managed perfectly well with 0.05 mg. daily, and a lesser number require 0.1 mg. and a still lesser number 0.2 mg. But most patients who take 0.2 mg. daily eventually develop toxicity which is very difficult to eliminate, as Dr. Eichna mentioned.

Since we are discussing the question of digitalization, intravenous and rapid, I should like to state that most of us hurry much too rapidly to digitalize the patient. The instances in which haste is necessary are very, very few. The instances in which some degree of urgency is valuable boil down to cases with auricular fibrillation and rapid ventricular rate. Those cases do not offer us a great problem in digitalization. On the other hand, patients with regular sinus rhythm who have congestive failure, need not be digitalized with great haste. In the first place, digitalis is rarely a dramatic drug in the treatment of cases with sinus rhythm, compared to other measures which we have. Secondly, it is in trying to digitalize such patients with regular sinus rhythm that we are apt to run into toxicity, in a futile effort to obtain a rapid, dramatic clinical improvement.

MODERATOR KOSSMANN: Ladies and Gentlemen, may I take just a moment to pull these remarks together for you? I think I may summarize them as follows: The addition of the glycosides to our therapeutic armamentarium in the management of the failing heart is a very real one, but one must not forget that even with the glycosides you still must do an animal assay except that the animal is your patient. Although it is of great advantage to have a preparation which has a fixed amount of active principle in it, nevertheless each patient requires an individual dosage and he must be, in a sense, biologically assayed with the drug. For the answer to the question, which preparation is the best, I think the gentlemen on the panel have made it clear that all of them have advantages, probably

all have certain disadvantages. For the practitioner it would appear wise to learn how to use one slow-acting preparation and one fast-acting preparation. Stick to those and you will find that your problems in the management of the failing heart will diminish, particularly the problem of getting the patient toxic, which seems to be the biggest difficulty when digitalis is used by the physician who is doing general practice.

Now, I have a whole handful of questions relating to digitalis and here is one that is rather important and touches on some of the remarks that Dr. Friedberg just made: Is it not a fact that patients with severe venous congestion sometimes do not respond to sufficient amounts of oral digitalis but do respond to parenteral digitalis? Would you like to discuss that, Dr. Friedberg?

DR. FRIEDBERG: I have not had that experience. I think it is a matter of time and dosage but where time is not an important element, I have not been able to find that parenteral digitalis will accomplish that which the oral will not.

MODERATOR KOSSMANN: *Dr. Batterman, would you like to say something?*

DR. BATTERMAN: I am in perfect accord with Dr. Friedberg. It is a question of time and dosage rather than one preparation having a superior effect upon the myocardium than the other. I think one thing has come out in the study of all the glycoside preparations. In terms of their action, —improvement of heart muscle efficiency,—whether you give them orally or by injection, they all act alike if equivalent dosages are used. It is a question of dose and not the speed of administration and not the glycoside that one uses.

MODERATOR KOSSMANN: *Dr. Eggleston, is bradycardia a contraindication to digitalis in the failing heart?*

DR. EGGLESTON: I think that depends upon the cause of the bradycardia or the type of bradycardia. If the bradycardia is due to a structural lesion in the bundle of His, so that when your patient is suffering from a complete A-V dissociation, it is no criterion at all. You don't need to use bradycardia as a measure for digitalization and those patients, if they are in congestive heart failure, can take the same digitalis dose as any other patient. Other bradycardias than that should be considered individually I believe.

MODERATOR KOSSMANN: *Along that same line, should digitalis be used in heart failure where there is complete heart block, with frequent*

Stokes-Adams' seizures?

DR. EGGLESTON: My answer to that would be, yes, you can use it.

MODERATOR KOSSMANN: *Is there any difference of opinion among the members of the panel?*

DR. FRIEDBERG: I don't think there is a real difference in my mind except that that type of case usually presents a much more acute problem with respect to the Stokes-Adams' syndrome. That problem is the measure which is the immediate indication for therapy. But if a patient in heart failure with an acute myocardial infarction had the Stokes-Adams' syndrome occurring frequently and if he were already on digitalis because of his heart failure, I would merely continue it and direct therapy to the control of the Stokes-Adams' attacks, that is with epinephrine.

MODERATOR KOSSMANN: *Dr. Eggleston, is digitalis of value in the patient with an enlarged heart without exertional dyspnea?*

DR. EGGLESTON: I think, Dr. Kossmann, that is a debatable point. It was thought by the Boston group of cardiologists that one might prevent further damage or further enlargement of the heart by the continued administration of digitalis in some one of its preparations. I don't think that there has been adequate evidence brought forth to support that contention. So I suppose I had better answer your question—no.

MODERATOR KOSSMANN: *Is there any difference of opinion among the members of the panel? Dr. Eichna?*

DR. EICHNA: May I make a comment on that? I agree completely with Dr. Eggleston and for what it is worth, the clinical investigator by measuring cardiac output has shown, and I refer now to Dr. Cournand and his group, that a large heart without congestive heart failure responds to digitalis in the same way as the normal heart, namely, a decrease in cardiac output rather than an increase in cardiac output, as is the case with congestive heart failure.

MODERATOR KOSSMANN: *Here is another question, which probably can be answered by Dr. Batterman: If moderately rapid digitalization is carried out orally with a shorter acting glycoside as Digoxin, how does one switch to digitalis leaf for further maintenance?*

DR. BATTERMAN: The assumption is you can get more rapid digitalization with one preparation orally than another and I think that is not exactly so. The rapidly acting glycosides only bring in the rapidity of action or the short latent period if you give them intravenously but if you give them orally, for clinical purposes, the speed of digitalization is

the same for all digitalis preparations. It takes anywhere from twelve to forty-eight hours, depending upon the dosage and the type of heart disease you have and you cannot obtain faster digitalization by using any particular preparation. But Dr. Kossmann's question brings up another fundamental fact and also emphasizes to some degree what Dr. Eggleston mentioned in terms of synergism. Any effect that you get from any one glycoside can be maintained by equivalent dosages of any other. If you should obtain complete digitalization with any preparation whether you obtain it by the parenteral or intravenous use, or orally, you can use any other preparation for maintenance in equivalent dosages. In other words, if you should have a patient who requires say 3.0 mg. of Digoxin for initial digitalization by the oral administration, the next day you can put that patient on 0.1 gm. of leaf and obtain the same effects as if you used a Digoxin dosage. Even though the Digoxin is rapidly dissipated from the body, the effects are not. The effects outlast the amount of the drug within the body.

MODERATOR KOSSMANN: *You have no further explanation for that, Dr. Batterman? It is confusing to many people how, with an excretory rate so much faster with the glycoside, you can maintain its action with a slower excreted preparation in equivalent dosage.*

DR. BATTERMAN: We have no explanation other than to point out that it is a very common experience in other pharmacologic actions of drugs that the action of a particular drug will outlast the amount of drug present within a cell or within an organ. I just have to bring to your attention the fact that if you give a local anesthetic for the treatment of neuritis, we know that procaine is very rapidly eliminated from the body and yet that painful state may be relieved as long as 24-48 hours. From a pharmacologic point of view, the action of the drug many times outlasts the presence of the drug within the body and the same thing holds true for digitalis preparations.

DR. EICHNA: It seems to me the problem is considerably different, Dr. Batterman. If you were to take a patient and digitalize him and then discontinued the medication, it might take you anywhere from weeks to months to find out what has happened to the patient before he reverts back into congestive heart failure. Therefore, the fact that you may go from one preparation to another preparation does not indicate that you have not actually allowed for excretion of the first dose and slowly built up with the second. It is not like a local anesthetic where the effect in

the skin is measured within the course of minutes. I agree that you can switch immediately from one drug to the other. I am not convinced of your explanation.

DR. BATTERMAN: May I continue?

MODERATOR KOSSMANN: Yes.

DR. BATTERMAN: Suppose you take a group of patients and digitalize them with digitalis leaf. If you should stop the use of digitalis at a point of toxicity and wait until that patient or group of patients returns to congestive failure, the average time is fourteen to sixteen days. That is the classic experiment for studying dissipation of effect because up to the time of radioactive digitoxin there has been no good chemical method of studying the amount of digitalis within the tissue. We study it in terms of returning congestive heart failure or return of tachycardia. If you take any such patient, if you know the rate of dissipation, say if he is going to go into failure on the fourteenth day, if you put such a patient on the maintenance dose a few days before, the patient will never go into failure even though you have completely eliminated the digitalis leaf as can be demonstrated by redigitalization at the end of a week. That patient can still maintain good cardiac reserve thereafter as long as the dissipation of effect has not been lost. In other words, if compensation is restored and that is what you are trying to do with any digitalis preparation, if that effect is not lost, a maintenance dose, which is nothing more than maintenance of compensation, will still continue to work.

Now let me give you another example because it has been quite confusing. In the days when ouabain or strophanthin was introduced there was considerable confusion as to how to put the patient on the maintenance dose of digitalis twenty-four hours later, because ouabain is very rapidly dissipated. As you know, if you did not give any more ouabain, four days later that patient or group of patients would be in congestive heart failure. Yet we know we can take that group of patients and give a full dose of ouabain or digitalis within twenty-four hours as though they had no ouabain previously.

It was thought that twenty-four hours after the initial digitalization with ouabain you had to start redigitalization. Actually it is not necessary, for as long as you have achieved compensation you can put that patient on a daily maintenance dose of any digitalis preparation and the patient will remain compensated and not lose that effect.

MODERATOR KOSSMANN: We have a lot of aspects of congestive

heart failure or the failing heart to consider from the therapeutic point of view. I am sorry we did not have time to answer all the questions on digitalis. *There is just one remaining question on digitalis that gives the practitioner a great deal of difficulty and I am going to ask Dr. Friedberg to answer it. If you have a heart that fails in the course of myocardial infarction, should you use digitalis?*

DR. FRIEDBERG: The answer would be yes, with this reservation that congestive failure needs some degree of definition. We define it in a rather broad sense. When acute myocardial infarction occurs there is a type of congestive failure in the sense that most patients with a severe infarction will have rales at the bases of the lungs and they may have some dyspnea. If this is defined as heart failure and if this is all there is, my tendency is not to use digitalis, because I regard this as merely a transient redistribution of the blood volume. However, if after several days, after the acute phase of shock and diminished cardiac output is passed, there is still evidence of congestive heart failure, as defined by symptomatology, then I use digitalis. I don't use it on the first day, not because I think it is dangerous, but because, as in many types of heart failure, the management of the causative factor is so much more important than the management of heart failure and I regard it as unwise to add another drug to those used in treating the infarction itself. For example, you know hyperthyroidism with heart failure is not really controlled unless you control the hyperthyroidism, etc., and so I wait a few days for readjustment of the myocardial infarction. Thereafter I give the drug if heart failure is present.

MODERATOR KOSSMANN: I would like to get into the mercurial diuretics a little bit because this, as I emphasized earlier in the hour, is probably one of the reasons why our patients with congestive heart failure stay around so long with us these days. *The first question I have here is: Can digitalis do anything for the failing heart which the mercurial diuretics cannot do? Dr. Eichna.*

DR. EICHNA: I don't have the answer. Perhaps to start the discussion I might simply describe several observations which we have been making. Patients are hospitalized with congestive heart failure. Hemodynamic determinations are made. The cardiac output is measured. The pressures behind the failing chambers are determined. The patient is then placed upon thiomerin, which we have chosen because it does not have the xanthine and we wish to get the diuretic effect alone. The patient has a

diuresis, loses weight, the venous congestion disappears, rales disappear and the liver gets smaller. A repeat study is done. Improvement in cardiac output is found. The pressure has returned to normal. If possible, the patient is exercised to determine his response to a work load. The patient is then digitalized with whatever preparation one may choose and when the patient has become toxic and then pulled back from toxicity, at least when we are sure he is fully digitalized, a third hemodynamic study is done. It is much too premature, Dr. Kossmann, but in about four or five patients so studied, we have found no hemodynamic difference between the second and third studies. This I realize is not an answer to your question. It does, however, raise an extremely pertinent point, namely, are we correct in our traditional concept that digitalis produces its effect by direct myocardial action. It will take long clinical observation on patients followed with diuretics alone to determine whether there is, or is not, a difference between patients treated solely with diuretics and patients treated with digitalis. This excludes patients who have arrhythmias because certainly if there is auricular fibrillation then digitalis is unquestionably the drug of choice.

MODERATOR KOSSMANN: Thank you, Dr. Eichna.

I think everyone is pretty much familiar with the clinically available mercurial diuretics but every once in a while there is a patient who does not respond to them or who becomes refractory. Dr. Batterman, what do we do when a patient becomes refractory to the mercurial diuretics?

DR. BATTERMAN: I would like to take it from a broader point of view, Dr. Kossmann, because in so doing, it is a little exception to what Dr. Eichna has stated. I have no argument with the dynamic observations.

DR. EICHNA: I simply stated an observation.

DR. BATTERMAN: I have no argument with the observations. I have observations from the clinical point of view. We were concerned with the effectiveness of diuretic agents and tried to determine from a practical point of view what could be the possible factor,—why patients have stopped responding to particular preparations when given in maximum dosage and given by various routes of administration. We found that heading the list was the fact that patients became refractory to mercurials if they were not on an optimum dose of a digitalis preparation. The heart is the central mechanism for heart failure and the so-called forward aspects produce a disturbance in kidney function so that you retain

sodium and therefore edema. If you haven't the central mechanism for maximum cardiac efficiency, the kidneys necessarily are not as effective. You can only obtain your maximum cardiac efficiency if you use the digitalis preparation adequately. In many of these patients adjustment of the dose of digitalis made the patient responsive to the mercurial. We have now been able to stop the mercurial because we have restored efficiency of the heart muscle.

I would like to point out this, when a patient goes into heart failure and there is a decreased efficiency of heart muscle, there is always some precipitating factor in such a patient. If you have removed the precipitating factor and restored the efficiency that existed prior to heart failure that heart should be as efficient as before. You can do that with digitalis. Under such circumstances the patient should no longer need any other therapeutic measure since you have restored normalcy. Many of these patients can now continue for many years on a daily dose of a digitalis preparation without needing any other therapeutic measure. It is when digitalis is less effective that other therapeutic measures are of help.

The second problem that arose in the use of mercurials was the question of exertion. Again this put an added load upon the heart so that the kidneys were less responsive. If we gave the mercurial diuretic to an ambulatory patient and had him walk around you could completely inhibit the diuresis whereas if the patient were at bed rest you will obtain a diuresis. The third factor is use of acidifying salts and I won't go into that at the moment because of time.

As to the presence of an excessive sodium restriction, if you haven't any sodium to be excreted you may not obtain diuresis. Other factors are low albumin or protein balance, and kidney function. We come back to the mercurial diuretic itself and its route of administration. If you give the maximum dose of a mercurial intramuscularly the best chance of getting a diuresis in a group of patients is no better than 60 per cent of your trials. In other words, 40 per cent of your patients will not respond, considering all factors which give you the maximum optimum result. If a patient does not respond to one mercurial intramuscularly, there is no point in trying another mercurial intramuscularly because you will get the same lack of response. You will either have to adjust the factors for lack of diuresis or use another parenteral route, giving it intravenously, which changes the amount of diuresis one obtains. It is also quicker. So, very often when the patient is refractory to the mer-

curial, it is because of the route of administration and the fact that there are other associated methods of treatment which are interfering with your diuresis. I omitted one other factor which is very commonly overlooked, chronic barbiturate administration. Phenobarbital or other sedatives which are commonly used in patients with heart failure will completely inhibit mercurial diuresis and if you decrease or stop the use of such preparations the patients may have a spontaneous response.

MODERATOR KOSSMANN: *Dr. Batterman, would you just say a word about the dangers of intravenous use of mercurials? There have been of course reports of death from the use of the preparation by this route. Also I recall, there have been several cases reported of death following the intramuscular route but there is a great reluctance of the physician in general practice to use the mercurials intravenously. Would you like to say a word about how he should give them if he must give them intravenously?*

DR. BATTERMAN: I think the history of the mercurial diuretics will give you the answer. The first mercurial diuretic was introduced in 1920, Novasurol, merbaphen. The first death due to its use was reported in the literature in 1925. That does not mean that death or reactions may not have occurred earlier but it did not hit the medical profession in terms of a report and so we have a five year "lag" period. This drug was used intravenously.

The next drug introduced, in 1924, was salyrgan, not with theophylline. The first death was reported in 1931, a seven year elapsed period. This drug also was used intravenously because it was very toxic by intramuscular injection.

The next drug introduced was novurit, mercuzanthin or Mercurophylline, in 1928. The first death for that was in 1933, five years later. That was also used intravenously. From 1940 to 1942 there was quite a furor about the occurrence of sudden deaths following the intravenous administration of the mercurials. Actually with the millions of injections that were used it was less than a fraction of a per cent, 40-50 such instances over a period of twenty years.

The next mercury diuretic introduced was mercuhydrin in 1945, and the intramuscular route was recommended as a safe procedure for this but the first death from mercuhydrin was reported in five years. This followed intramuscular administration.

The next was thiomerin in 1949, but because the basic chemical

structure of this is the same as mercurophylline, replacing the xanthine by a mercaptal group, you may obtain reactions to this if the patient has reactions to mercurophylline.

Now a new mercurial has been introduced, known as Cumertilin, and from the basis of past experience you can expect that within five years there will be a death or a reaction. It has to occur. The point I am trying to make is that deaths are dependent upon the basic chemical structure of all these products and you have to build up a sufficient number of patients over many years of use before you may obtain reactions or toxicity and it is immaterial which route of administration you use. If your patient has a reaction, then you should turn to another mercurial diuretic and not to a change in the route of administration.

MODERATOR KOSSMANN: Thank you, Dr. Batterman. Time is running out faster than I expected it would. *There are many aspects of the problem that we have not covered, so I am going to ask just one more question on the mercurials and then go on to one or two other aspects of the management of the failing heart. It concerns the oral mercurials. I am sure you have all been receiving in your mail numerous advertisements regarding the use of the oral mercurials. Would you say a word about that, Dr. Batterman? Do the oral mercurial diuretics have a place in the management of the failing heart?*

DR. BATTERMAN: Yes, only in the sense that they are used for maintenance, not for replacement of the parenteral injections. They cannot be used in the same conditions where one desires a rapidly dehydrating action in the patient. They cannot give you the same degree of diuresis, the same predictability of diuresis, no matter what dose you use by oral administration but if a patient accumulates edema rapidly and requires a parenteral injection twice a week or three times a week, then a daily dose of an oral preparation will decrease the accumulation of the edema to the point where one can decrease the number of injections. One should use rest periods in the sense that the patient should be given a few days of cessation of the use of the orally administered preparations every three weeks. The dose is one or two tablets every day, never to exceed that, because you will not achieve any greater diuresis with more. It takes several weeks before you achieve the effect you are looking for, the slow prevention of accumulation of edema.

DR. FRIEDBERG: You regard all the mercurials, that is, the oral ones, as being equal when you mentioned dosage?

DR. BATTERMAN: Equal in the sense of what one would obtain from accumulation but not toxicity. There are some more toxic than others. Neohydrin is, in my experience, the most toxic, having the greatest incidence of gastrointestinal irritation. Next is salyrgan-theophylline, Mercurophylline and the least toxic of all is the latest one, Cumertilin.

MODERATOR KOSSMANN: *I think we have to leave this very interesting aspect of the management of this syndrome to go on to three other aspects I would like the Panel to cover with you in the few minutes left. One is in relation to the electrolyte disturbances which occur with the failing heart and which will plague the physician, particularly in the terminal phases of the disease but which may occur at any time in the course of the disease, particularly if diuretic therapy is overenthusiastic. I have this question: May intractable heart failure be due to electrolyte disturbances and how should it be treated?*

Will you handle that, Dr. Friedberg?

DR. FRIEDBERG: The answer to this question of necessity must be given with reservations. We are making statements about electrolyte disturbances which I think will require revision. In general we say that if the mercurials are given very frequently and if at the same time the patient's sodium intake is low he may develop disturbances in the blood electrolyte pattern. These disturbances may be of two major types. In the first, the sodium is not substantially altered in its concentration from the level of about 140 mEq. per liter, but the chlorides are substantially below the normal of 103 or thereabouts, in other words, a chloride level below 90 or 80 mEq. per liter. At the same time there is usually also an alkalosis, as has been noted by elevation in bicarbonate, and frequently also a diminution in potassium. In such patients who develop what we call a hypochloremic alkalosis, with hypokalemia, the response to treatment is often very poor. Correction of the electrolyte pattern by the administration of ammonium chloride, preferably by mouth, supplemented by potassium if indicated by the low serum potassium concentration may result in a favorable clinical response. I should like to emphasize, both with respect to this and the next aberration in electrolytes, that one is often hard pressed to determine to what extent the clinical picture is the result of the electrolyte disturbance or whether these electrolyte disturbances do not develop more readily because we are dealing with a patient with such advanced heart failure that it is refractory to treatment.

The second abnormal electrolyte pattern is one in which both serum sodium and chloride concentrations are low and usually there is a mild acidosis associated with it. This is the so-called low-sodium syndrome. It is not necessarily due to depletion in the sense that much sodium is lost by diuresis. Many of these patients who are on low sodium intake virtually excrete no sodium in the urine. But they are taking fluids ad lib and so we have a dilution of the serum sodium, since the sodium excreted is not being replaced because the sodium intake is so low. These patients develop a very serious syndrome characterized by many clinical features, including nausea, apathy, or even stupor. They may go into shock. They may develop azotemia and they look as if they are moribund. Theoretically the indication is for hypertonic sodium chloride in an effort to correct the deficient electrolytes. Sometimes there is a temporary improvement. But a strikingly favorable result is infrequent because the low sodium syndrome is only partly due to the low sodium intake and the vigorous mercurial therapy but more especially is due to the patient's very poor cardiac state. That may be because the myocardium has reached an irreversible degree of heart failure. But it is often due to the fact that some of the therapeutic measures, a few of which were listed, were not properly carried out. In other words, if I might add one word to the treatment of refractory heart failure, it is to be sure first that you have eliminated all the contributory causes such as hyperthyroidism, etc., and other basic contributory diseases, and secondly that each of the measures utilized in the treatment of heart failure, rest, digitalization, sodium restriction, etc., has really been carried out as meticulously as you think it should be. In the average patient with heart failure, you can get away with a good deal, even though some of the measures are not perfectly executed but when you come to a patient who is very seriously ill with heart failure, any imperfection, whether over- or under-digitalization, over- or under-mercurialization, etc., will result in refractoriness and in these electrolyte disturbances.

MODERATOR KOSSMANN: Thank you, Dr. Friedberg.

A few weeks ago at one of the Cornell Conferences there was a discussion about the cation exchange resins. In that conference I understand that Dr. Eggleston made a statement that he could not get his patients to take "that clay." You see he is a little bit biased, but I am going to ask him a question. Dr. Eggleston, what part do you think the cation exchange resins play in the management of the failing heart?

DR. EGGLESTON: Dr. Kossmann, in my practice very little. The same statement that I made at the Cornell Conference holds today. I find it very difficult to get the patient to take with any degree of regularity enough of the cation exchange resins to accomplish any useful purpose and since those patients are already having a great many troubles, some of which are greater than their inability to take the cation exchange resin, I don't try to force them. I hope that the chemists will soon provide us with something more readily consumed by the patient.

MODERATOR KOSSMANN: *Is there any other opinion of the panel?*

DR. FRIEDBERG: Yes, I would like to venture an opinion. I find that in the type of patient that we see in the hospital (and that may not be representative because the patient is usually sent in because he is very refractory to treatment), in whom a really low sodium intake is essential for therapy, the use of the cation resin is extremely important and extremely valuable. I agree with Dr. Eggleston that clay is a very generous description of both the appearance and taste of the resins, but I believe that some of the newer preparations, even though they go by the same name, are more palatable and much more manageable and I feel that when the patient is sick enough, it is a very useful adjunct to other therapeutic measures. That does not mean that it is a routine necessity in the vast majority of patients with heart failure, just as it is not a routine necessity to limit sodium intake to 200 mg. a day in the average patient with heart failure who will do well with only moderate restriction.

MODERATOR KOSSMANN: *Just one last question—I think everyone will agree that even though oxygen makes up 20 per cent of the atmosphere, it is rather expensive when you get it in a hospital for a patient, and as I understand from Dr. Eichna, the patient with congestive heart very rarely shows an arterial oxygen saturation that is much below normal. In view of this apparent paradox is there a need for oxygen in the treatment of the failing heart, Dr. Eichna?*

DR. EICHNA: Very briefly, only in the severely ill patient. Remember that if you increase the oxygen concentration in the inhaled air, some of that oxygen will go into solution in the plasma in addition to being carried by the hemoglobin. That oxygen dissolved in plasma is available and will be made available to the tissues and consequently will permit a better oxygen transport to the tissues in the face of the lowest cardiac output that these patients have.

MODERATOR KOSSMANN: *Are there any other remarks from the panel?*

DR. BATTERMAN: I would like to mention another action of oxygen which is sometimes overlooked and that is it has a sedative effect. Patients in heart failure that have apprehension and have marked anxiety can be quieted by the use of oxygen. It is also an analgesic in a sense that the patients have less pain in the chest, less difficulty in breathing in using the accessory muscles. So even though you may decrease the dyspnea, and it may not be reflected in the change in oxygen saturation, from a therapeutic point of view these patients have subjective improvement.

DR. EICHNA: I would like to disagree with Dr. Batterman again. Oxygen does not have a sedative effect, Dr. Batterman. What it does do is to combat the cerebral hypoxia which is the factor which causes the patients to be restless. You see I mentioned that the oxygen in solution is available and it is available to the brain in these instances and it will frequently give the brain enough oxygen with its poor blood supply in order that the patient no longer has the disorientation, the restlessness and so on. I agree with you thoroughly with regard to the result in the therapeusis again, but I disagree with the explanation. Frequently the patients will do better if you put them in the oxygen tent as you say, rather than give them a barbiturate which will make them worse.

DR. BATTERMAN: I have no argument with the method of action with which I agree with Dr. Eichna. I am saying in terms of general value we see a sedative action which Dr. Eichna indicates.

MODERATOR KOSSMANN: Ladies and Gentlemen, the time is up. I must thank you for your enthusiastic participation in this panel and I regret that we were not able to answer all of your questions because of the lack of time. I also would like to take this opportunity on behalf of the Academy of Medicine to thank the members of the panel for giving us their expert opinions this afternoon.

SOPHOCLES CONTRA FREUD: A REASSESSMENT OF THE OEDIPUS COMPLEX*

IAGO GALDSTON

THE theoretical edifice of Freud's psychoanalysis is resplendent with many conceptions and formulations. Freud was not only a master of the word, he was also skilled in the use of analogy. He was even more apt in the invention of provocative, startling, and suggestive terms and phrases with which to epitomize and to label significant components of his theoretical system. Thus, for example, Freud did not merely call attention to the sexuality of the child, but further described the child as a polymorphous, perverse little animal. The expression anal-erotic not only aptly described the compulsively fixated individual, but was calculated to stir and rattle the Victorian generation. What could better describe the Id than the term "Id"; the elemental, the primitive, the *uralt*. And as for the Super-ego—how could you name it better? Certainly conscience is not its equivalent, for conscience is all-too-much the policeman and does not include, as Super-ego does, the aspiratory element. How apt are the expressions "transference neurosis," and how suggestive and translucently illuminating is the term "counter-transference." *Abreaktion* is a harsh Germanic term, for which the more mellifluous Latin and Anglo-Saxon tongues provide no equivalent, but the very sound of that term is in itself suggestive.

Indeed, as one observes the superb skill with which Freud manipulated terms and expressions, one cannot but become suspicious that through this art Freud at times unwittingly seduces our reason. By the aptness of his terms he leads us to believe that there is vastly more of knowledge and certainty behind his verbal formulations than we do indeed find there, when in a less dazzled mood we soberly inspect their meaning content.

In affirming all this, I would not have you believe that Freud deliberately set out to mislead us, or that I would charge him with a kind of

* Presented at a combined meeting of the Section on Neurology and Psychiatry of The New York Academy of Medicine and the New York Neurological Society, January 12, 1954.
Manuscript received January 1954.

verbal charlatanry. On the contrary, with deep respect for his genius, I intend only to underscore the fact that often there was more poetry than science in his expositions, and that frequently, even though his arguments were poor and his deductions faulty, his theme and thesis were of transcending import.

Contrary to the insistence of certain medical historians psychiatry is a very ancient discipline, in some respects even antedating clinical medicine itself. Yet despite the antiquity of psychiatry Freud's psychoanalysis stands forth as a unique achievement, as unique as Pasteur's germ theory, and Claude Bernard's homeostasis. Still, psychoanalysis did not spring like Minerva from the head of Zeus; it has its antecedents, or at least its antecedent components. Freud's psychoanalysis is a compact system,—logically, historically and clinically structuralized. But it is more singular in its formulation than in its elements. The Unconscious, which plays so significant a role in psychoanalytic theory, was known before Freud. The tripart constitution of personality, the Id, the Ego, and the Super-ego, though not thus named, was known to all psychologists since the time of Aristotle, and formed a prominent and integral part of the doxy of the Catholic Church. The significance and the function of dreams had been the preoccupation of many men, and in Plato's *Republic* one finds an illuminating reference to the upwelling, during sleep, of the uncensored cravings of the primal self from out of the depths of the Unconscious. Even the technique of free association was expounded by Galton, Darwin's grandson and the Nestor of genetics.

In tracing the building blocks of the Freudian system to the intellectual and scientific quarries from which they were derived, I do not aim to dim the lustre of Freud's originality. Quite the contrary! This exposition is but a prelude to my treatment of the most distinguished and the most original element in the Freudian system. I refer, of course, to the Oedipus complex. Though many before Freud treated of dreams, of the Unconscious, of free association, of the significance of slips and errors, one needs must go back to the days of Plato, and to the times of Sophocles to find the subject of the Oedipus complex expounded clearly and boldly.

Freud fully appreciated the pre-eminence of the theory of the Oedipus complex in the theoretical framework of psychoanalysis. In his psychoanalytic testament[1] he wrote: "I venture to assert that if psychoanalysis could boast of no other achievement than the discovery of the

repressed Oedipus complex, that alone would give it a claim to be counted among the precious new acquisitions of mankind."

The analytic world concurs in Freud's assessment of the Oedipus complex, and holds it to be nuclear for personality development. Surveying the broad field of contemporary psychiatric thought, not only as it is formulated by Freud and his disciples, but also as it has been cultivated by the so-called Freudian deviationists and by those others who, though not disciples of Freud, are yet inspired and instructed by the data of dynamic psychiatry, one finds that the understanding and interpretation of the Oedipus complex is crucial to all systems of psychiatric theory, and to all the different patterns of their praxis. *Nolens volens* they each must take their stand on this score. This is indeed clearly reflected in a work recently published by Mullahy, entitled *Oedipus: Myth and Complex*.[2] This work reviews and summates the different interpretations, the differences in accent and assessment which the more significant psychiatric schools of thought have accorded to the Oedipus myth and complex.

The Oedipus complex is indeed nuclear to personality development, and for that reason commands the most earnest, the most devoted, and the most penetrating study. I intend to contribute to this objective, by reassessing the Oedipus complex. I want to counterpose Sophocles' treatment of the Oedipus Myth in the fifth century B.C. to Freud's exposition of it 2,400 years later. Since I have entitled this presentation *Sophocles contra Freud* it is evident that I think there is some difference, and it *is* my intention to demonstrate not only that Freud misread the tragedy of Oedipus as represented by Sophocles, but that he has drawn certain psychological lessons from the Oedipal Myth which are not there to be drawn.

Freud dealt with only one of the three plays which Sophocles devoted to the Myth of Oedipus. He based his elaborate deductions on the single play *Oedipus Rex*. But Sophocles wrote three plays involving Oedipus—*Antigone*, *Oedipus Rex*, and *Oedipus at Colonus* and, be it noted, in just this order. For the contemporaries of Sophocles, the Oedipal Myth was not entirely embraced in the tragedy of *Oedipus Rex*. *Oedipus Rex* mirrors but a portion of the "crimes and punishment" of the House of Labdacus. The incest of Oedipus was not the beginning of the tragedy of the House of Labdacus, but its mid-point. It highlights the Nemesis that followed upon the ubris of the House of Labdacus.

The incest of Oedipus was not an initial crime but a consequent to the crimes of the father. *Oedipus Rex*, *Oedipus at Colonus*, and *Antigone* collectively portray the Greek version of the warning in *Exodus* that "the iniquity of the fathers shall be visited upon their children even unto the third and fourth generation." (Exodus, XX-5.)

At this point it is desirable to fix in our minds the essential plot of *Oedipus Rex*. Laius, the father of Oedipus and the husband of Jocasta, was without issue. He consulted the Oracles and was informed by them that if a son were born to him, he, Laius, would die at the hand of his son. In due time a son was born to Laius and Jocasta. That child, later named Oedipus, was, on the third day following his birth, turned over by his mother Jocasta, to a shepherd with instructions that he be cast away to perish. But Oedipus did not perish. He was discovered by another shepherd and brought to the childless King of Corinth, Polybus, by whom he was raised as his own son. Then when Oedipus was grown to the stature of a man, stirred by doubt, Oedipus consulted the Oracle at Delphi. The Oracle revealed to him that he was fated to be "the slayer of the sire who begot him" and "to defile his mother's bed." Seeking to escape his destiny, and still believing that Polybus was his father and Merope his mother, Oedipus fled Corinth, hoping thus "to never see the fulfilment of the infamies foretold by his evil doom." But during his flight, at the meeting of three roads, Oedipus was rudely thrust aside by the herald of a man "seated in a carriage drawn by colts." In anger he struck down first the driver and then the old man who had assaulted him with his goad. This old man, unknown to Oedipus, was his very own father Laius, King of Thebes.

In his further wanderings, Oedipus encountered the Sphinx, that chimerical creature half woman, half tiger, who had besieged the land, and who destroyed all those who could not answer the riddle: "What is that creature that in its infancy walks on four members, in its maturity on two, and in its age on three?" Until Oedipus appeared none had unravelled her riddle and Thebes was sorely grieved. But when the Sphinx challenged Oedipus he made the right answer saying—that creature is man, who in his infancy moves on his four members, in maturity on his two feet, and in age supports himself with a staff. Her riddle solved, the Sphinx threw herself upon the rocks and perished. Thebes was liberated and to reward him the Thebans made Oedipus their King and gave him Jocasta for a wife. Out of this incestuous relationship four

children were born, two sons and two daughters. Thebes prospered for a time but then a plague broke out in the city, and Thebes was once again sorely stricken. Oedipus consulted the soothsayers and was by them advised that the city was punished because the murderer of Laius had not been found nor was his death avenged. Hearing this Oedipus took an oath pledging himself to discover and to punish the murderer of Laius. Ultimately, by the witness of the shepherd to whom he was given as an infant, and by that of the other shepherd who brought him to the childless King of Corinth, Oedipus is revealed to have been the murderer of his father and to have had incestuous relations with his mother.

Following on these catastrophic revelations Jocasta hanged herself, and Oedipus struck out his eyes. Led by his two daughters he went forth in exile.

This is the essential story of *Oedipus Rex*. The Myth itself is of ancient derivation. It was known long before Sophocles embodied it in his magnificent tragedy. There were several versions of the Myth extant in which the destiny of Oedipus was differently rendered. But these other versions need not concern us, for Freud took his line of departure from the *Oedipus Rex* of Sophocles. This Greek tragedy according to Freud mirrored, what he believed to be, a universal phenomenon: the desire of the young child to have incestuous relations with his mother, and to destroy the father who stood in the way of their attainment.

Freud maintained that every child is fated to pass through the Oedipus complex. This is what Freud has to say on this score:

"When a boy, from about the age of two or three, enters upon the phallic phase of his libidinal development, feels pleasurable sensations in his sexual organ and learns to procure these at will by manual stimulation, he becomes his mother's lover. He desires to possess her physically in the ways which he has divined from his observations and intuitive surmises of sexual life and tries to seduce her by showing her the male organ of which he is the proud owner. In a word, his early awakened masculinity makes him seek to assume, in relation to her, the place belonging to his father, who has hitherto been an envied model on account of the physical strength which he displays and of the authority in which he is clothed. His father now becomes a rival who stands in his way and whom he would like to push aside. If when his father is absent he is able to share his mother's bed and if when his father returns

he is once more banished from it, his gratification when his father vanishes and his disappointment when he reappears are deeply felt experiences. This is the subject of the Oedipus complex, which Greek legend translated from the world of childhood phantasy into a pretended reality. Under the conditions of our civilization it is invariably doomed to a terrible end."[3]

Let me underscore the fact that Freud does not merely affirm that the child has a strong attachment to the mother. Freud specifically says that the little boy "desires to possess her [the mother] physically in the ways which he has divined from his observations and intuitive surmises of sexual life": in other words, that he specifically desires to have sexual intercourse with her. Freud ascribes to the young child what I would call *infantile* incestuous desires. These are to be distinguished from the incestuous desires of the adult.

Upon this basic assumption Freud then builds an intricate superstructure involving the so-called castration fear, the resolution of the Oedipus complex, and the concomitant flowering forth of the Super-ego. It is best to quote Freud's own words on these scores. After having described what he believes to be the universal infantile incestuous strivings of the young boy, Freud goes on to say:

"The boy's mother understands quite well that his sexual excitement refers to her. Sooner or later she thinks to herself that it is wrong to allow this state of things to continue. She believes she is acting rightly in forbidding him to manipulate his genitals. The prohibition has little effect and at the most brings about some modification in his method of self-gratification. At last his mother adopts the severest measures; she threatens to take away from him the thing he is defying her with. As a rule, in order to make the threat more terrifying and more credible, she delegates its carrying out to the boy's father, saying that she will tell him and that he will cut the penis off. Strangely enough, this threat only operates if another condition is fulfilled, either before or afterwards. In itself it seems quite inconceivable to the boy that anything of the sort could happen. But if when he is threatened he is able to recall the appearance of female genitals, or if shortly afterwards he has a glimpse of them—of genitals, that is to say, which really lack this supremely valued part, then he takes what he has heard seriously and coming under the influence of the castration complex, experiences the severest trauma of his youthful existence."[4]

Whatever else one might say about Freud's primary and secondary elaborations on the Oedipus complex, one must grant that they are most ingenious! But their very ingenuity renders them suspect. Freud premises the sequential concatenation of many events, and one is impelled to wonder just how often this chain of events is likely to be linked in just that way. And what happens if one of the links is missing or is "out of order." What, if the mother does not adopt the severest measures to forbid the child to manipulate his genitals? What, if she does not threaten "to take away from him the thing he is defying her with." What, if she does not tell the father of the son's disobedience, and what happens when she does not threaten the child that the father will cut his penis off. What, if the child does not see the female genitalia until he is much older, or, seeing them is not shocked at all.

The more critically one studies the tortured formulations of Freud's theory of the Oedipus complex, the more inescapable is the conviction that in this instance Freud was traduced by his daring and betrayed by his ingenuity. Did Freud read aright the myth of Oedipus? Does the story of *Oedipus Rex* told by Sophocles really warrant Freud's deduction? Freud himself appears to be aware of certain difficulties, for he admits that the plot of the tale "constitutes a deviation from the analytical subject matter since Oedipus killed his father and married his mother unknowingly." But Freud, having noted these difficulties, seeks to evade them by propounding nebulous generalizations on poetic principles. Freud writes:

"One hears the objection made that the legend of King Oedipus has in fact no connection with the construction made by the analysis: the case was quite a different one, since Oedipus did not know that it was his father whom he killed and his mother whom he married. What is overlooked in this is that a distortion of this kind is unavoidable if an attempt is made at a poetic handling of the material, and that there is no addition of extraneous subject matter but merely a skillful employment of the factors present in the theme."[5]

In the light of what we know of the Greek playwrights' ingenuity and of their boldness, one must wonder what warrant there may be for Freud's categoric statement that "a distortion of this kind is unavoidable in the poetic handling of the material." Freud was a great psychiatrist, but one must question his competences as a literary critic and as a dramaturge, the more so when one observes a footnote to the above

cited paragraph, wherein Freud ventures the opinion "that the name William Shakespeare is most probably a pseudonym behind which there lies concealed a great unknown."[6]

Did Freud interpret the Myth of Oedipus correctly? My conviction is that he did not. Freud distorted the meaning of the Myth to suit his preconceptions. That is a great pity, for the Myth of Oedipus is pregnant with great meaning, and Freud, having misread it, perpetrated a double injury: the promulgation of his own errors and the blocking of a proper understanding of the meaning of the Myth.

Let us see how the Myth is treated by Sophocles. Sophocles wrote three plays which involve the parents and the children of Oedipus, *Antigone*, *Oedipus Rex*, and *Oedipus at Colonus*. These plays, be it noted, do not really constitute a trilogy in the traditional sense of that term. Sophocles did not pick up the theme at its beginning and follow it through its logical course. Actually he wrote on the last part first. He composed the tragedy of *Antigone* before he wrote *Oedipus Rex* and *Oedipus at Colonus*. However, in the three plays Sophocles portrays the bitter fate and the cruel destinies of the House of Labdacus.

To understand just what Sophocles intended to convey in these plays one needs to visualize the author and his plays in the setting of his land and times. One must appreciate the function of drama in Greek society. One must know the moral and philosophical bias of the contemporary thought. This would be a vast undertaking were we called upon to forge it for ourselves. Fortunately such is not the case for we can draw upon the knowledge and understanding of many pre-eminent scholars ranging from Plato and Aristotle, to Gilbert Murray and Werner Jaeger.

Sophocles was one of the three great dramatic poets in Greek culture. He stood between Aeschylus who was thirty-five years his senior, and Euripides who was fifteen years his junior. He lived in the golden era of Greek culture; in the fifth century B.C. He was a contemporary and friend of Pericles. He was by the witness of those who knew him an extraordinary person, wise, temperate, and a sober observer of human beings. It was said that Aeschylus wrote of man as he ought to be, and Sophocles of man as he was. Here it is proper to inquire what was the function of the dramatic poet in the Greek society of the fifth century. To understand that we must needs know what it was that troubled the minds of the Greeks of this period.

Werner Jaeger[7] offers a direct and succinct answer to this question.

"The Greeks of the sixth and fifth centuries," he writes, "had long been brooding on the great religious problem: why does God send suffering into the life of man?" During the preceding centuries it was commonly believed that man was the plaything of the gods and that man's destiny reflected no more than the caprice of the Olympians. When Aesop was asked what was Zeus engaged in, he answered: "In humbling the exalted and in exalting the humble."[8] In the purview of Aesop, the gods were jealous of man, and they smote him at will to keep him humble. But in the fifth century B.C. this common and primitive viewpoint was challenged by the dramatic poets. Aeschylus expounded the moral thesis that each man fares according to his deserving, that even the individual life, viewed in its happiness and misery, is long enough to justify the ways of God to man. In the tragedies of Aeschylus, Nemesis or divine justice displaces divine jealousy.[9] Not the gods but man himself is the ultimate arbiter of his destiny. For the exposition of this lesson on the selfhood of man the dramatic poets chose as vehicles the great myths of Greece. Werner Jaeger phrased it thus: "Tragedy was the first type of poetry to apply to mythical tradition a regular structural principle—the conception of the inevitable rise and fall of human destiny, with its sudden reversals and its final catastrophe."[10]

The theatre was the great teaching institution of the Greek populace. The dramatic poets taught the man of the Greek polis to recognize the tie between crime and punishment. Instead of thinking of man as the helpless plaything of the Gods, he came to see him as the arbiter of his own destiny and hence the begetter of his own misery.

This newer persuasion raised the stature of man. It imparted dignity to his person, and provided him with the foundation for a sound morality. But it also made more acute the problem of fate and of free will. It brought to the fore the soul-stirring questions of corporate guilt, and of long deferred punishment. Most of all it evoked that most troubling query—"Wherefore are the innocent children guilty and punishable for the transgressions of the sinful father?"

This was a problem that no less agitated the Hebrew prophets than the dramatic poets of Greece. For it had been said among the descendants of Abraham that the sins of the father shall be visited upon his children even unto the third generation. True, it was not entirely clear whether the children were to be punitively afflicted for their father's sins, or whether the children of the transgressing father would perforce suffer

the inevitable consequences of their father's sins. The prophet Ezekiel (Chapter 18) rejected the first interpretation and freed the notion of moral responsibility from all ties of blood relationship. "What mean ye, that ye use this proverb, The fathers have eaten sour grapes, and the children's teeth are set on edge? . . . The soul that sinneth it shall die. The sons shall not bear the iniquity of the father, neither shall the father bear the iniquity of the son."

According to Plutarch, Euripides also boldly accused the gods of grave injustice in visiting the sins of the parents upon the children. The moral indignation of the prophets is noble and inspiring. But the sober-eyed poets were troubled by the witness of that which could be construed only as the unassuaged operations of a malignant hereditary curse. Life and legend told of numerous families in which, because of some ancestral crime, the taint of guilt was transmitted in the blood, and generation after generation was visited by the anger of the gods.

This was the problem that stirred the souls of the dramatic poets, and to this problem both Aeschylus and Sophocles devoted their genius and their skills.

Aeschylus appears to have been the less clear in his mind on these issues. He argued that not actual guilt but the tendency to guilt is inherited. He deemed man the master of his own fate, for a man could foster the tendency to guilt, or he could resist it. An act of will, said Aeschylus, is necessary to wake the curse into life.[11] But in his dramatic presentations Aeschylus for the most part portrayed "the natural continuity of guilt." In *Agamemnon* (Lines 758-60) Aeschylus affirms: "The impious deed leaves after it a progeny, all in the likeness of the parent stock."

The main burden of the tragedies of Aeschylus is "that as crime engenders crime in the individual heart, so in a house the guilt of the fathers tends to lead the children into new guilt and to extend itself over a whole race."[12]

This torturing problem, the weight of the sins of the father upon the destinies of the children, lies at the core of the Sophoclean plays. This is the issue about which revolve the tragedies of Oedipus. *Oedipus Rex*, *Oedipus at Colonus*, and *Antigone* set forth in majestic proportions the calamitous interplay of sin and suffering in parent and child. From this purview it is patent that the incest of Oedipus was not an initial crime but rather a derivative punishment, and that this punishment gave

issue in turn to other crimes.

Freud appears to have completely missed this. In *Oedipus Rex* Sophocles exhibits the utmost depths of degradation, patricide and incest, to which the son may be reduced whose father and mother are unmindful of their moral obligations.

Let us look more closely at the tragic destinies of the House of Labdacus. We begin with Laius, the father of Oedipus. He was childless and had inquired of the Oracle as to the prospects of issue. He was told that if he had a son, he would lose his life by the hand of his own child. There is in this prophecy of the Oracle a something of transcendent depth and meaning, for if the prophecy is understood not in its literal but in its symbolic sense, then it becomes clear that every father is consumed in his parenthood and that every son "displaces" his father in the love of the mother. But that aside, and even assuming that the prophecy is to be understood in its literal rather than in its symbolic meaning, then still are Laius the father and Jocasta the mother of Oedipus guilty of murder. For on the third day after his birth Oedipus, bound in foot, was given to a shepherd, to be cast away to perish.

Here then is the initial crime. It engendered a progeny of other crimes. It led to the destruction of Oedipus, of his parents Laius and Jocasta, and of his progeny.

To grasp the full import of the tragedy of *Oedipus Rex*, we need to ask, as Sophocles appears to have asked, what might have happened if, despite the prophecy of the Oracle, Laius and Jocasta had rejoiced in the birth of their son, and had nurtured him in love and care. Might not then the fates have been mollified? Might not the transcending goodness, and the enduring virtue of Laius have served as an all-encompassing shield against the dire menace of the outrageous prophecy?

I have advisedly said that Sophocles *appears* to have asked these questions, for Sophocles was not an Isaiah. He wrestled with, he defined and clarified, but did not resolve the moral issue expounded in his tragedies. Yet even though he does not give a clear nor ultimate answer to the Why of Oedipus' fate, he pleads his partial innocence. When in the play *Oedipus at Colonus*, Oedipus is taunted by the Chorus he defends himself passionately and with pathos.

To the Chorus Oedipus says:

"I have suffered misery, strangers,—suffered it through unwitting deeds, and of those acts—be Heaven my witness!—no part was of mine

own choice."

When Creon, the brother of Jocasta, names him "a patricide,—a polluted man,—a man with whom had been found the unholy bride of her son," Oedipus speaks this soul-searing speech:

"O shameless soul, where thinkest thou falls this thy taunt,—on my age, or on thine own? Bloodshed—incest—misery—all this thy lips have launched against me,—and all this I have borne, woe is me! but no choice of mine: for such was the pleasure of the gods, wroth, haply, with the race from the old. Take me alone, and thou couldst find no sin to upbraid me withal, in quittance whereof I was driven to sin thus against myself and against my kin. Tell me, now,—if, by voice of oracle, some divine doom was coming on my sire, that he should die by a son's hand, how couldst thou justly reproach me therewith, who was then unborn,—whom no sire had yet begotten, no mother's womb conceived? And if, when born to woe—as I was born—I met my sire in strife, and slew him, all ignorant what I was doing, and to whom,—how couldst thou justly blame the unknowing deed?"[13]

And yet though Oedipus was not knowingly guilty of the crimes of patricide and incest, he was guilty of obdurate impiety—of what the Greeks termed *nosos phrenoon* a frenzy of the spirit that hastened his destruction. This is witnessed in numerous passages but nowhere more forcefully than in *Oedipus at Colonus*. When Antigone, the daughter of Oedipus, pleads for her brother Polyneices who has come to beg for Oedipus' blessings, Oedipus refuses to see him. Antigone, addressing her father, says:

"Thou art his sire; so that, e'en if he were to wrong thee with the most impious of foul wrongs, my father, it is not lawful for thee to wrong him again.

"Look thou to the past, not to the present,—think on all that thou hast borne through sire and mother; and if thou considerest those things, well I wot, thou wilt discern how evil is the end that waits on evil wrath; not slight are thy reasons to think thereon, bereft, as thou art, of the sight that returns no more."[14]

Oedipus yields, but instead of blessing Polyneices, he curses him and his brother:

". . . begone, abhorred of me, and unfathered!—begone, thou vilest of the vile, and with thee take these curses which I call down on thee—never to vanquish the land of thy race, no, nor ever return to hill-girt

Argos, but by a kindred hand to die, and slay him by whom thou hast been driven out."[15]

In this curse lies the doom of his sons and also the seed of the fatal tragedy of Antigone.

Tempting though it is to pursue further the destinies of the House of Labdacus, I must limit myself to the exposition already made: and *that*, I feel certain, fully supports the conclusion that Freud failed to grasp the meaning of the Sophoclean play *Oedipus Rex*. I will not reargue the argument, but merely cite the conclusion. The patricide and incest of Oedipus were not *his* crimes, but the dire consequences of the guilts of Laius, his father, Jocasta, his mother, and of Oedipus' own *ubris*. There is nothing in *Oedipus Rex* to justify Freud's contention that the play expounds the universality of the infantile incest wish. This play, and the other two, teach quite another lesson, one that reflects on the father rather than on the son, that has to do with moral fortitude, with love, with charity and with mercy, rather than with sexuality in general, and with infantile incest longings in particular.

But here another problem comes to the fore. Granting that Sophocles does not support Freud's theories on infantile incest, may it not be that they are yet valid—even without Sophocles' consent? Perhaps Freud's only error was to call on the *Oedipus Rex* for witness. This query transposes the problem of the infantile incest wish from out the realm of the Greek tragic poets into that of a clinical psychiatry. Now we need to inquire not what Sophocles said and meant, but rather what experience teaches. But here again we are confronted with the witness of the side effects of Freud's ingenuity in coining terms and phrases. His inventions are like some highly polished objects which, because they are so very scintillating, render it difficult to discern their contours and to define their borders. Freud's terms, Oedipus Complex, Castration Fear, and Penis Envy, are so convenient and suggestive that in wide usage they have outrun the confines of the meaning originally given them by Freud. Thus many psychiatrists who do not at all subscribe to Freud's ideas on infantile incest, employ the term Oedipus Complex to describe the sensually determined affect bond between mother and child, and between child and father.

Castration Fear, and Castration Complex are very apt terms wherewith to describe psychological emasculation. Yet their usage does not bind one to the literal meaning of castration. Penis Envy hardly means

the subjective wish for the objective virile member, but describes rather discontent with, fear and rejection of, femininity and in consequence an envy of male prerogatives, most often without any real comprehension of what those prerogatives imply.

In canvassing the experience and judgment of psychiatrists it is imperative that we should be alert to the fluidity in meaning with which many psychoanalytic terms in general, and the Oedipus Complex in particular are used.

It is correct to say that only the devout and worshipful disciples of Freud still accept his dicta on the Oedipus Complex in their pristine form. Most others, as Mullahy[16] has clearly shown, differ from Freud, some few in minor, and the greater number in major respects. Neither Alfred Adler nor Jung accept Freud's version of the Oedipus Complex. Otto Rank obfuscates it with his theories on the Birth Trauma. Erich Fromm, who has devoted much thought and study to the Oedipus Complex sees it "not as a symbol of the incestuous tie between mother and son, but as the rebellion of the son against the authority of the father." Sullivan, while assigning a determining role to the parents and especially to the mother, in the "shaping of the child," rejects the idea that the role is a sexual one, even in the wide sense in which Freud conceives of sexuality. Karen Horney is even more outspoken; not only does she reject Freud's formulation of the Oedipus Complex but argues further that Freud's classic formulation can have dangerous consequences. For while we are preoccupied with the alleged infantile incest wish we are prone to overlook the most important of all of the child's needs—interest in, and respect for, the child, and the necessity for real warmth, reliability and sincerity by the parents.

The consensus of clinical psychiatric experience does not support Freud's contentions that every little boy desires to physically possess his mother "in the ways which he had divined from his observations and intuitive surmise of sexual life." Freud's formulation of the Oedipus Complex as the universal and specific infantile incest wish, must be rejected as unproved and in error. And yet, this does not quite dispose of it. The curtain is not thus to be rung down on Sophocles—nor on Freud either. We are impelled to temper the finality of our judgment with Galileo's immortal phrase: *E pure si muove*. This concept *is* vital: it stirs and is stirring, if not with the vision of Freud, then with that of Sophocles. Yet Freud cannot be counted out, for it was *his* inspiration

to link the Sophoclean tragedy with the dynamics of the child's psychic growth, with its maturation and with the growth of its Super-ego. Moses, with whom Freud nurtured a deep identification, did not enter the Promised Land, but it was he who led the enslaved hordes through the wilderness to the very gates of the Promised Land.

In the Oedipal Myth there is embodied the concept of the parental matrix within which the nascent personality and the psyche of the child is nurtured and fashioned. Where there is love of parent for parent, and yet so much free scope as to include in the embrace of affection also the child, there the child will effectively learn how to fulfill the tasks and to meet the challenges of its own growth and maturation, and reciprocally will bear affection for the parents. But where the parents themselves are immature, and encumbered with neurotic reaction and behavior patterns; where the father knows not how, or is unable to function as male, husband and father, or the mother will not or cannot play her reciprocal roles, there indeed is the child most likely, nay, bound to suffer.

It is this simple yet vital validity that lies at the core of the Oedipal Myth—and not the fancied incest wish of the child. Whosoever, day in day out, treats with those troubled in spirit and mind, with the sick that come to the psychiatrist for help, cannot but recognize that he confronts in his patients not the sins of the children but "those of the fathers." And he must be mindful also that the problem with which Sophocles wrestled confronts him likewise this day, for when he has helped the patient to lay bare the past, to gain insight, he must further help him also to act upon his insight. Thus the psychiatrist is at one with Sophocles in holding that the individual's destiny is fashioned not alone by what happens to him but also by what he does about it.

REFERENCES

1. Freud, S. *An outline of psychoanalysis.* New York, W. W. Norton & Co., 1949, p. 97.
2. Mullahy, P. *Oedipus: myth and complex.* New York, Hermitage Press, 1948.
3. Freud, S. Reference 1, pp. 90-91.
4. Freud, S. Reference 1, pp. 91-92.
5. Freud, S. Reference 1, p. 95.
6. Freud, S. Reference 1, p. 96.
7. Jaeger, W. W. *Paideia;* translated from the 2nd German edition by Gilbert Highet. New York, Oxford University Press, 1945, v. *1*, p. 251.
8. Butcher, S. H. *Some aspects of Greek genius.* London, Macmillan & Co., 1904, p. 107.
9. Butcher, S. H. Reference 8, p. 109.
10. Jaeger, W. W. Reference 7, p. 254.
11. Butcher, S. H. Reference 8, p. 116.
12. Butcher, S. H. Reference 8, p. 117.
13. Mullahy, P. Reference 2, p. 437.
14. Mullahy, P. Reference 2, pp. 443-444.
15. Mullahy, P. Reference 2, p. 448.
16. Mullahy, P. Reference 2, chapters 6-11.

TWENTY-SEVENTH ANNUAL GRADUATE FORTNIGHT

THE NEW YORK ACADEMY OF MEDICINE

2 East 103 Street, New York

INFECTIONS AND THEIR MANAGEMENT

OCTOBER 18–29, 1954

EVENING LECTURE PROGRAM

MONDAY, OCTOBER 18

PRESIDENTIAL ADDRESS
ALEXANDER T. MARTIN

METABOLIC DETERMINANTS OF INFECTION
Ludwig Kast Lecture
RENE J. DUBOS, Member, Rockefeller Institute for Medical Research

CURRENT METHODS IN THE TREATMENT OF TUBERCULOSIS
Harlow Brooks Lecture
J. BURNS AMBERSON, Professor of Medicine, College of Physicians and Surgeons, Columbia University

TUESDAY, OCTOBER 19

ALTERATIONS IN PATHOLOGY IN INFECTIONS SINCE THE INTRODUCTION OF CHEMOTHERAPY AND ANTIBIOTICS
Wesley M. Carpenter Lecture
PAUL R. CANNON, Chairman, Department of Pathology, The University of Chicago, Chicago, Illinois

ACUTE NON-PURULENT MENINGITIS
YALE KNEELAND, JR., Associate Professor of Medicine, College of Physicians and Surgeons, Columbia University

WEDNESDAY, OCTOBER 20

EVALUATION OF IMMUNOLOGIC METHODS IN THE CONTROL OF POLIOMYELITIS
THOMAS FRANCIS, JR., Professor and Chairman, Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor, Michigan

VIRAL HEPATITIS
RODERICK MURRAY, Assistant Chief, Laboratory of Biologics Control, National Microbiological Institute, National Institutes of Health, Bethesda, Maryland

THURSDAY, OCTOBER 21

THE ROLE OF A NEW GROUP OF PREVALENT VIRUSES IN UNDIFFERENTIATED RESPIRATORY ILLNESSES
ROBERT J. HUEBNER, Chief, Section on Virus and Rickettsial Diseases, Laboratory of Infectious Diseases, National Microbiological Institute, National Institutes of Health, Bethesda, Maryland

INTERACTIONS OF HOST, MICROBE AND CHEMOTHERAPEUTIC AGENT
COLIN M. MacLEOD, Professor of Microbiology, New York University College of Medicine

FRIDAY, OCTOBER 22

THE EPIDEMIOLOGY OF HEMOLYTIC STREPTOCOCCAL INFECTIONS
C. H. RAMMELKAMP, Professor of Medicine, Western Reserve University Medical School and Director of Streptococcal Disease Laboratories, Warren Air Force Base, Wyoming

THE USE OF ANTIBIOTICS FOR THE PREVENTION OF RHEUMATIC FEVER
GENE H. STOLLERMAN, Medical Director, Irvington House; Instructor in Medicine, New York University College of Medicine

(Program continued on following pages)

MONDAY, OCTOBER 25

CURRENT STATUS OF THE DEVELOPMENT OF ANTIMICROBIAL AGENTS
GLADYS L. HOBBY, Ph.D., Research Division, Chas. Pfizer & Co., Inc., Brooklyn, N. Y.

THE COMPLICATIONS OF ANTIBIOTIC THERAPY
LOUIS WEINSTEIN, Associate Professor of Medicine, Boston University School of Medicine and Lecturer on Infectious Diseases, Harvard Medical School

TUESDAY, OCTOBER 26

HORMONES AND INFECTION
LEWIS H. THOMAS, Professor of Pediatrics and Medicine, The Pediatric Research Laboratories of the Heart Hospital, University of Minnesota Medical School, Minneapolis, Minnesota

STAPHYLOCOCCUS INFECTIONS
VERNON KNIGHT, Associate Professor of Medicine, Vanderbilt University Medical School, Nashville, Tennessee

WEDNESDAY, OCTOBER 27

LOW RESISTANCE TO INFECTIONS: RELATIONSHIP TO ABNORMALITIES IN GAMMA GLOBULIN
DAVID GITLIN, Instructor in Pediatrics, Harvard Medical School

PRESENT DAY CONSIDERATIONS OF THE RABIES PROBLEM
HORACE L. HODES, Director, Department of Pediatrics, The Mount Sinai Hospital; Clinical Professor of Pediatrics, College of Physicians and Surgeons, Columbia University

HISTOPLASMOSIS
C. W. EMMONS, Ph.D., Mycologist, National Microbiological Institute, U.S. Public Health Service; Professorial Lecturer, George Washington University Medical School, Washington, D.C.

THURSDAY, OCTOBER 28

THE ACUTE DIARRHEAL DISEASES OF BACTERIAL ORIGIN
F. S. CHEEVER, Professor of Microbiology, Graduate School of Public Health, University of Pittsburgh

EVALUATION OF DIAGNOSTIC TESTS IN INFECTION
CALDERON HOWE, Associate in Microbiology, College of Physicians and Surgeons, Columbia University

FRIDAY, OCTOBER 29

APPROACHES TO THE CHEMOTHERAPY OF VIRAL INFECTIONS
FRANK L. HORSFALL, JR., Member, Rockefeller Institute for Medical Research

ANTIBIOTIC THERAPY OF VIRAL AND RICKETTSIAL DISEASES
JOSEPH E. SMADEL, Director, Division of Communicable Diseases, Army Medical Service Graduate School, Walter Reed Army Medical Center, Washington, D.C.

REGISTRATION FEES—NON-FELLOWS

Fellows of The New York Academy of Medicine will be furnished registration cards without application and without fee. A registration card will be sent to Non-Fellows upon receipt of check, payable to *The New York Academy of Medicine*, for $10.00 for the entire program, $6.00 for *either the first or second week.*

Medical Officers of the Armed Services, in uniform, will be admitted without charge.

Interns and Residents will be admitted without charge, provided they present letters from their Chiefs of Service. They will be seated as facilities permit, after Fellows of the Academy and other registrants have been accommodated.

(Program continued on following pages)

TWENTY-SEVENTH ANNUAL GRADUATE FORTNIGHT

MORNING PANEL PROGRAM

11:00 A.M. at the Academy

First Week

Monday, October 18

FEVER OF UNDETERMINED ORIGIN

Chairman: Hamilton Southworth

Members: J. Burns Amberson
Joseph H. Burchenal
Yale Kneeland, Jr.
Currier McEwen

Wednesday, October 20

LOCAL USE OF ANTIBIOTICS AND PROTEOLYTIC ENZYMES IN SURGICAL INFECTIONS

Chairman: Louis M. Rousselot

Members: William A. Altemeier
Edward L. Howes
W. Ross McCarty

Friday, October 22

MANAGEMENT OF NON-TUBERCULAR PULMONARY INFECTIONS

Chairman: Dickinson W. Richards

Members: Alvan L. Barach
Perrin H. Long
William S. Tillett

Second Week

Monday, October 25

THE MANAGEMENT OF REGIONAL INFECTIONS

Chairman: Yale Kneeland, Jr.

Members: David V. Habif
John K. Lattimer
Carl T. Nelson
Louis Weinstein

Wednesday, October 27

COMBINED MEDICAL AND SURGICAL TREATMENT OF TUBERCULOSIS

Chairman: Walsh McDermott

Members: Aaron D. Chaves
James G. Hirsch
Herbert C. Maier
Carl Muschenheim
Robert Yeager

Friday, October 29

THERAPY OF AMEBIASIS AND OTHER PARASITIC INFECTIONS

Chairman: Harry Most

Members: Harold W. Brown
B. H. Kean
Elmer H. Loughlin
Howard B. Shookhoff

TWENTY-SEVENTH ANNUAL GRADUATE FORTNIGHT

HOSPITAL CLINICS PROGRAM

CALENDAR OF CLINICS

All Clinics will be held from 2 to 5 P.M.

First Week

Monday, October 18	1. Flower-Fifth Avenue *Hospital Representative:* DAVID LEHR
Tuesday, October 19	2. Mount Sinai *Hospital Representative:* SOLOMON SILVER
Wednesday, October 20	3. Veterans Administration (Bronx) *Hospital Representative:* JULIUS WOLF
Thursday, October 21	4. Presbyterian *Hospital Representative:* HARRY M. ROSE
	5. Polyclinic Hospital *Hospital Representative:* JAMES P. CROCE
Friday, October 22	6. St. Vincent's *Hospital Representative:* C. G. DE GUTIERREZ-MAHONEY

Second Week

Monday, October 25	7. Bellevue *Hospital Representative:* ALPHONSE TIMPANELLI
Tuesday, October 26	8. Willard Parker* *Hospital Representative:* JEROME L. KOHN
Wednesday, October 27	9. New York *Hospital Representative:* RALPH TOMPSETT
Thursday, October 28	10. St. Luke's-Woman's *Hospital Representative:* CHARLES G. ADSIT, JR.
Friday, October 29	11. Lenox Hill *Hospital Representative:* ARTHUR F. ANDERSON

* This clinic *only*, will be held at the Academy; all others at the designated hospitals.

SCIENTIFIC EXHIBIT

As in past years, a comprehensive Scientific Exhibit will be an integral part of the 1954 Fortnight.

MEDICAL RESEARCH FORUM

to be held by

THE NEW YORK ACADEMY OF MEDICINE

2 EAST 103 STREET • NEW YORK 29, N. Y.

THE NEW YORK ACADEMY OF MEDICINE will hold a Forum for Medical Research during the coming academic year 1954-1955. By accepting only a limited number of presentations of new and original work, the Committee hopes to present an interesting program of current clinical research. Investigators may present results of original research in clinical medicine at this Forum, to be held Wednesday, January 26, 1955, at 8:00 P.M.

This Forum is being arranged by the Committee on Medical Education of the Academy with the following stipulations:—

1. **Presentations will be confined to *recent* original research in clinical medicine, surgery, or to research which is applicable to medicine or surgery in all clinical branches.**
2. **Presentations should be reports of work done within the last year or of progress in a continuing project. Previous submission to or presentation before a society will not prejudice the opportunity for presentation at the Forum.**
3. **In submitting applications, the investigator is requested to state whether this work has been published, in toto or abstract, or has been submitted for publication; also, in cases where the investigator is working under the head of a department of a hospital or research institute, approval of the head of department is requested.**

Presentations will be limited to twelve minutes. A period of free discussion will follow each presentation.

The publication of presentations is not a necessary condition but the Academy plans to publish promptly abstracts of presentations, if the author so desires. In order to expedite publication of abstracts, the Committee requests that the abstract submitted by the investigator be carefully prepared in the form in which publication is desired, with the understanding that publication of the abstract in the *Bulletin* of the Academy shall not preclude publication by the author in any other journal.

The Committee extends an invitation to all research workers of Greater New York to submit *an abstract of proposed presentation in QUADRUPLICATE*, not to exceed 500 words in length, to the Secretary of the Committee on Medical Education of the Academy *during September and October 1954 and not later than November 1, 1954.* A formal invitation to participate in this program will then be extended by the Committee to the authors of papers selected for presentation.

ROBERT L. CRAIG, M.D., *Executive Secretary*
Committee on Medical Education
The New York Academy of Medicine

MONTHLY PANEL MEETINGS ON THERAPEUTICS FOR THE GENERAL PHYSICIAN

Third Series

1954—1955

Fridays at the Academy—4:30 P.M.

NOVEMBER 5, 1954 — **HEADACHE: ITS ETIOLOGY AND MANAGEMENT**
Moderator: H. HOUSTON MERRITT

DECEMBER 3, 1954 — **THE STATUS OF SURGERY IN THE MANAGEMENT OF CARDIAC CONDITIONS**
Moderator: CLARENCE DE LA CHAPELLE

JANUARY 7, 1955 — **PREVENTIVE USE OF PSYCHOTHERAPY IN CHILDHOOD**
Moderator: LAWRENCE S. KUBIE

FEBRUARY 4, 1955 — **THE EFFECTS OF TOBACCO SMOKING**
Moderator: To be announced

MARCH 4, 1955 — **PARKINSON'S DISEASE: MEDICAL AND SURGICAL MANAGEMENT**
Moderator: SAMUEL BROCK

APRIL 1, 1955 — **MANAGEMENT OF PANCREATITIS**
Moderator: CHARLES F. WILKINSON, JR.

THE NEW YORK ACADEMY OF MEDICINE
2 EAST 103 STREET • NEW YORK 29, N. Y.

POSTGRADUATE RADIO PROGRAMME OF

THE NEW YORK ACADEMY OF MEDICINE

arranged by THE COMMITTEE ON MEDICAL INFORMATION

in cooperation with THE COMMITTEE ON MEDICAL EDUCATION

and THE NEW YORK CITY CANCER COMMITTEE

THURSDAYS – 9:00 P.M. – 10:00 P.M. Station WNYC-FM – 93.9 megs.

OCT. 7 THE ACTION OF DRUGS AND TOXIC AGENTS ON THE BLOOD PICTURE—(Panel)—Paul Reznikoff, *Moderator, Professor of Clinical Medicine, Cornell University Medical College, New York* with Roy E. Albert, Charles A. Doan, Leonard J. Goldwater and Claude Forkner.

PRESENT TRENDS IN THE TREATMENT OF CANCER OF THE BREAST—Herbert C. Chase, *Professor of Clinical Surgery, New York Medical College, Flower & Fifth Avenue Hospitals, New York.*

OCT. 14. CLINICAL IMPLICATIONS OF PLASMA FRACTIONATION—I. Herbert Scheinberg, *Assistant Professor of Medicine, College of Physicians & Surgeons, Columbia University, New York.*

DIAGNOSES AND MANAGEMENT OF MEDIASTINAL TUMORS —Irving S. Shiner, *Assistant Professor, Department of General Surgery, New York Medical College, Flower & Fifth Avenue Hospitals, New York.*

OCT. 21 CURRENT CONCEPTS IN THE MANAGEMENT OF THE MENOPAUSE, FEMALE AND MALE—(Panel)—Howard C. Taylor, Jr., *Moderator, Professor and Chairman, Department of Obstetrics and Gynecology, College of Physicians & Surgeons, Columbia University, New York,* with Frederick Randolph Bailey, Robert S. Hotchkiss, Charles M. McLane and S. Bernard Wortis.

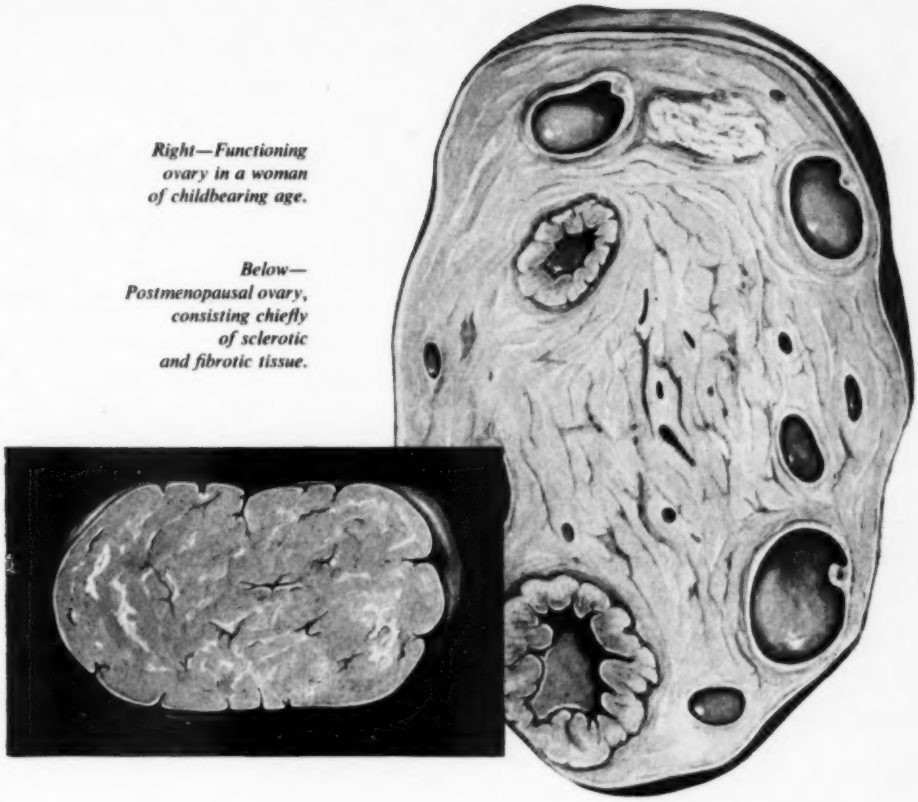
THE ROLE OF RECONSTRUCTIVE SURGERY IN FACIAL CANCER—Clarence S. Straatsma, *Associate Professor, Department of Otolaryngology, New York Medical College, Flower & Fifth Avenue Hospitals, New York.*

OCT. 28 SURGERY OF ACQUIRED VALVE LESIONS—Robert H. Wylie, *Professor of Clinical Surgery, College of Physicians & Surgeons, Columbia University, New York.*

THE CLINICAL SIGNIFICANCE OF HOARSENESS—Bernard J. Wattiker, *Instructor, Department of General Surgery, New York Medical College, Flower & Fifth Avenue Hospitals, New York.*

Right—Functioning ovary in a woman of childbearing age.

Below—Postmenopausal ovary, consisting chiefly of sclerotic and fibrotic tissue.



"Target action" in Vallestril® therapy

Vallestril is described as having "target action" because it provides potent estrogenic activity *only in certain organs.*

Vallestril combines a potent action on the *vaginal mucosa* with minimal effect on the *uterus or endometrium.*

This distinctive, *selective* action helps explain the unusually low incidence of withdrawal bleeding as reported in recent carefully controlled studies. For this reason alone, Vallestril is preferentially indicated in the therapy of the menopausal syndrome.

Vallestril "quickly controls[1] menopausal symptoms, ... The beneficial effect of the medication appeared within three or four days in most menopausal patients. There is also evidence that the patient can be maintained in an asymptomatic state by a small daily dose, once the menopausal symptoms are controlled."

The dosage in menopause is one tablet (3 mg.) two or three times daily for two or three weeks; then reduced to one or two tablets daily as long as required.

[1]Sturnick, M. I., and Gargill, S. L.: Clinical Assay of a New Synthetic Estrogen: Vallestril, New England J. Med. *247*:829 (Nov. 27) 1952.

SEARLE Research in the Service of Medicine

WHEN SYMPTOMS ARE DISTRESSING BUT DISGUISED . . .

"It is strange," Malleson says, "how little clinical recognition" has been given to the "negative behavior" or "endogenous misery" of the woman with endocrine imbalance. Largely accountable for this, of course, is the patient's own reluctance to discuss these symptoms with her physician until she actually suffers from some of the more obvious menopausal symptoms such as hot flushes. Even then she may become so accustomed to her change in feeling she can't remember what it's like to feel well.[1]

Changes in the mood pattern are just a few of the many distressing symptoms of declining ovarian function which are so often disguised because they do not always coincide with cessation of menstruation, and at times will occur long before, and even years after. Other good examples are insomnia, headache, easy fatigability, arthralgia — and understandably so, when one considers that the loss of ovarian hormone "withdraws one of the most important metabolic regulators of the organism."[2]

"Premarin" is a preparation of choice for the replacement of body estrogen. "Premarin" presents a *complete* equine estrogen-complex and all the components of this complex are meticulously preserved in their natural form. This largely explains why "Premarin" not only produces prompt symptomatic relief but also imparts an important "plus" — the distinctive "*sense of well-being*" that patients find so highly gratifying. These benefits of "Premarin" have made it a natural estrogen widely prescribed by physicians . . . and often preferred by patients.

"PREMARIN."®

ACCEPTED COUNCIL ON PHARMACY AND CHEMISTRY AMERICAN MEDICAL ASSOCIATION

has no odor
. . . imparts no odor

Estrogenic Substances (water-soluble), also known as conjugated estrogens (equine), available in both tablet and liquid form

1. Malleson, J.: Lancet 2:158 (July 25) 1953. 2. Goldzieher, M. A., and Goldzieher, J. W.: Endocrine Treatment in General Practice, New York, Springer Publishing Company, Inc. 1953, p. 23.

NEW YORK, N. Y. Ayerst MONTREAL, CANADA

The long and short of Bentyl's relief of nervous gut

Clinicians[1,2] prove Bentyl is long on effective relief... short on unwanted side effects including blurred vision and dry mouth.

1. McHardy and Browne: Sou. Med. J. 45:1139, 1952. 2. Lorber and Shay: Fed. Proc. 12:90, 1952.

Complete Bentyl bibliography on request.

BENTYL

(Bicyclomine Hydrochloride)

another exclusive development of Merrell research

Rx INFORMATION

BENTYL

Bentyl affords direct (musculotropic) and indirect (neurotropic) spasmolytic action. Bentyl provides complete and comfortable relief in smooth muscle spasm; particularly in functional G.I. disorders, in irritable colon, pylorospasm, biliary tract dysfunction and spastic constipation.

Composition: Each capsule or teaspoonful (5 cc.) contains 10 mg. of Bentyl (dicyclomine hydrochloride).
Bentyl with Phenobarbital adds 15 mg. of phenobarbital to the preceding formula.

Dosage: *Adults,* 2 capsules or 2 teaspoonfuls of syrup, three times daily, before or after meals. If necessary, repeat dose at bedtime. *In Infant Colic,* ½ to 1 teaspoonful, ten to fifteen minutes before feeding.

Supplied: Bentyl — In bottles of 100 and 500 blue capsules, and Bentyl Syrup in pint and gallon bottles. Bentyl with Phenobarbital — In bottles of 100 and 500 blue-and-white capsules, and Bentyl Syrup in pint and gallon bottles.

Merrell
Since 1828
PIONEER IN MEDICINE FOR OVER 125 YEARS

THE WM. S. MERRELL COMPANY New York • CINCINNATI • St. Thomas, Ontario

Herald Square, N. Y.

Parkchester, Bronx *Jamaica, Queens*

White Plains, N. Y. *Flatbush, Brooklyn*

MACY'S PRESCRIPTION DEPARTMENT

Macy's respects professional ethics. We carefully avoid discussing your prescription, either its ingredients or its use, with your patient. You can be assured that all your prescriptions are accurately compounded exactly as you write them. And all our preparations, made from the finest ingredients obtainable, are carefully checked by our supervising pharmacists.

No wonder so many physicians prefer Macy's Prescription Department.

For acidosis due to anesthesia — edema

KALAK

Counter-Acts

ANTI-BIOTIC REACTIONS

. . . . KALAK is a non-laxative, alkaline diuretic buffer — side reactions from aureomycin — terramycin — sulfas — penicillin are reduced through the use of KALAK — KALAK contains only those salts *NORMALLY* present in plasma. . . . IT IS BASIC!

KALAK WATER CO.
of NEW YORK, Inc.
90 West St., New York 6, N. Y.

For acidosis due to nausea — in nephritis

BULLETIN

THE NEW YORK ACADEMY OF MEDICINE

The Bulletin contains scientific papers presented at the Academy, including . . .

Graduate Fortnight Lectures
Stated Meeting Addresses of the Academy
Academy Section Papers
Section on Microbiology—Abstracts
Forum for Clinical Research—Abstracts
Monthly Panel Meetings—Transcripts
New York Pathological Society—Abstracts
and
Other Original Contributions

Published Monthly

Annual subscription price, $6.50 in United States and Canada.
All other countries $7.50

Calm AND *Relaxed*

WITH **MEBARAL®**

The calming influence of Mebaral is eminently helpful in

- tension and anxiety states
- nervous symptoms of the menopause
- neurasthenia
- mild psychoses
- hysteria
- hyperthyroidism
- migraine
- pruritus
- hyperemesis nervosa
- hyperemesis gravidarum
- restlessness and irritability associated with pain or infection
- cardiovascular disorders
- allergies
- alcoholism

WINTHROP

DOSAGE:

Adults—32 mg. to 0.1 Gm. (optimal 50 mg.), 3 or 4 times daily.

Children—16 to 32 mg., 3 or 4 times daily.

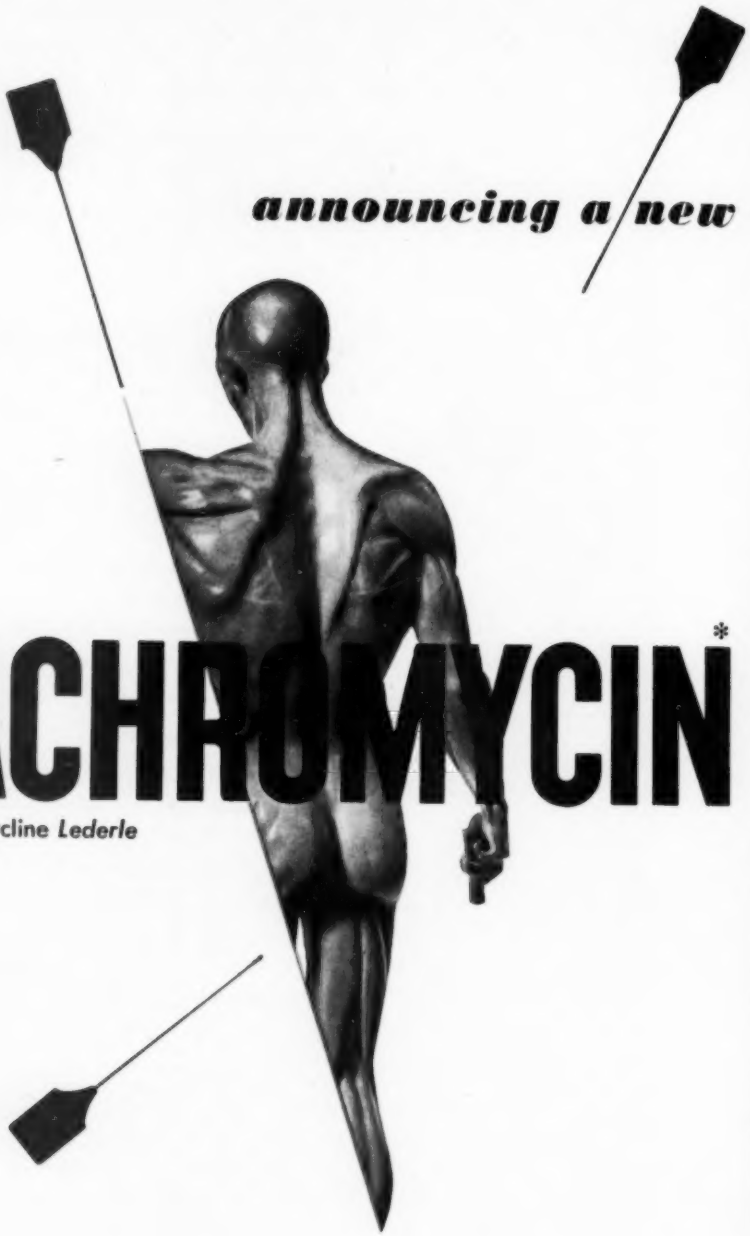
HOW SUPPLIED:

Tablets of 32 mg. (½ grain)
Tablets of 50 mg. (¾ grain)
Tablets of 0.1 Gm. (1½ grains)
Tablets of 0.2 Gm. (3 grains) scored for division

Winthrop-Stearns INC.
New York 18, N. Y. Windsor, Ont.

Mebaral, trademark reg. U. S. Pat. Off., brand of mephobarbital

announcing a new



ACHROMYCIN*

Tetracycline *Lederle*

therapeutic advance

At last, the many advantages of intramuscular administration of a broad-spectrum antibiotic have been fully realized. ACHROMYCIN, since its recent introduction, has been notably effective in oral and intravenous dosage forms. Now, after clinical testing, it is definitely proved highly acceptable for intramuscular use.

INTRAMUSCULAR

IMMEDIATE absorption and diffusion
PROMPT CONTROL of infection
CONVENIENT for the physician
NO UNDUE DISCOMFORT for the patient.

This new intramuscular form widely increases the usefulness of ACHROMYCIN, the broad-spectrum antibiotic of choice.

ACHROMYCIN Intramuscular is available in vials of 100 mg.

Lederle

*REG. U. S. PAT. OFF.

LEDERLE LABORATORIES DIVISION
AMERICAN Cyanamid COMPANY Pearl River, New York

when proper or corrective shoes are indicated . . .

***prescribe* PEDIFORMES**

IN STOCK:

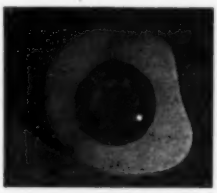
- straight last shoes
- inflare last shoes
- outflare last shoes
- club foot shoes
- flat foot shoes
- childen's shoes with Thomas Heel and long counter

You are assured alterations and fittings as you prescribe because of our interest, and experience gained in serving the medical profession for more than 40 years.

Pediforme

34 West 36th STREET
New York City
Wisconsin 7-2534

Other Shops in: Brooklyn • Flatbush • Hempstead
New Rochelle • Hackensack



SATISFACTION GUARANTEED

Specialists in Plastic and Glass Artificial Human Eyes Exclusively

Referred Cases Carefully Attended

FRIED & KOHLER, Inc.

665 FIFTH AVENUE near 53rd Street
NEW YORK, N. Y. Tel. ELdorado 5-1970

CHARLES B. TOWNS HOSPITAL *Established 1901*

FOR THE TREATMENT OF ALCOHOLISM

NARCOTIC AND BARBITURATE

ADDICTIONS EXCLUSIVELY

Complete Medical & Psychiatric Treatment at predetermined cost. Privacy of patient is assured—if desired.

Literature on Request

Edward B. Towns, *Director*

293 Central Park West, N. Y. 24, N. Y.
SChuyler 4-0770

Member American Hospital Association

PHOTOGRAPH BY VICTOR KEPPLER

The gouty arthritic plays again...

BENEMID®

PROBENECID

When you treat your gouty arthritic patient with BENEMID, "lessening of joint disability and swelling"[1] follows the reduction (or even disappearance) of old tophi. In less advanced cases, crippling gouty arthritis has been prevented and "further enlargement of tophi" has been retarded.[1]

Patients on BENEMID therapy have returned to useful occupations,[1] even when these have required skilled use of the hands.[2]

BENEMID accelerates the excretion of uric acid.[3] "No instances of refractoriness [have been] reported."[3] Toxic reactions are rare.

Quick Information: Available in 0.5 *Gm.* tablets. *Dosage:* 1 to 4 tablets daily. *Contraindication:* renal impairment.

References: 1. Indust. Med. 22:311, 1953. **2.** J.A.M.A. 149:1188, 1952. **3.** Bull. Vancouver M.A. 29:306, 1953.

THESODATE

THE ORIGINAL ENTERIC-COATED TABLET
OF THEOBROMINE SODIUM ACETATE

provides
EFFECTIVE
WELL-TOLERATED
PROLONGED
VASO-DILATION

in
CORONARY
ARTERY
DISEASE

REPEATEDLY SHOWN and proven by objective tests on human subjects[1] — this is one of the most effective of all the commonly known Xanthine derivatives. Because of the enteric coating it may be used with marked freedom from the gastric distress characteristic of ordinary Xanthine therapy. Thus THESODATE, with its reasonable prescription price also, enjoys a greater patient acceptability.

Available: **In bottles of 100, 500, 1000.**

TABLETS THESODATE

*(7½ gr.) 0.5 Gm. (*3¾ gr.) 0.25 Gm.

THESODATE WITH PHENOBARBITAL

*(7½ gr.) 0.5 Gm. with (½ gr.) 30 mg.
(7½ gr.) 0.5 Gm. with (¼ gr.) 15 mg.
*(3¾ gr.) 0.25 Gm. with (¼ gr.) 15 mg.

THESODATE WITH POTASSIUM IODIDE

(5 gr.) 0.3 Gm. with (2 gr.) 0.12 Gm.

THESODATE, POTASSIUM IODIDE WITH PHENOBARBITAL

(5 gr.) 0.3 Gm., (2 gr.) 0.12 Gm. with (¼ gr.) 15 mg.

***In capsule form also, bottles of 25 and 100.**

1. Riseman, J. E. F. and Brown, M. G. Arch. Int. Med. 60: 100, 1937
2. Brown, M. G. and Riseman, J. E. F. JAMA 109: 256, 1937.
3. Riseman, J. E. F. N. E. J. Med. 229: 670, 1943.

For samples just send your Rx blank marked — 20 TH 10

Brewer
EST. 1852

BREWER & COMPANY, INC. WORCESTER 8, MASSACHUSETTS U.S.A.

produces contractions

*"clinically identical to normal, strong, physiological labor"**

PITOCIN®

AN OXYTOCIC OF CHOICE

PITOCIN is widely used in obstetrics because of its physiologic effect on uterine musculature. In addition, the fact that it is notably free from vasopressor action is often a significant advantage. Intravenous administration of diluted **PITOCIN** in emergencies makes possible ready control of dosage and response.

PITOCIN is valuable in treatment for primary and for secondary uterine inertia, for postpartum hemorrhage due to uterine atony, for the third stage of labor, for induction of labor, and during cesarean section to facilitate suturing the uterine wall.

*Kaufman, R. H.; Mendelowitz, S. M., & Ratzan, W. J.: *Am. J. Obst. & Gynec.* 65:269, 1953.

PITOCIN (oxytocin injection, Parke-Davis) is supplied in 0.5-cc. (5-unit) ampoules, and in 1-cc. (10-unit) ampoules, in boxes of 6, 25, and 100. Each cc. contains 10 international oxytocic units (U.S.P. units).

MEDICAMENTA VERA

Parke, Davis & Company

DETROIT, MICHIGAN

4 out of 5 former fatties...

gain it right back!

the *Am Plus*® **post-diet plan**

for the 80%
who fail to sustain
weight loss
*after the diet**

*Aaron, H.: *Weight Control*, Consumer Reports 17:100 (Feb.) 1952.

Just one AM PLUS capsule daily, taken when hunger becomes excessive: before the day's "big" meal, before a club lunch or dinner, at snack time. The patient decides when.

A unique combination of dextro-amphetamine plus the original formula of 19 important vitamins and minerals, AM PLUS rehabilitates post-dieting habits while it augments nutritional intake.

536 Lake Shore Drive, Chicago 11, Illinois

In spastic and occlusive vascular diseases

TENSODIN

Tensodin Tablets
100's, 500's and 1000's

Tensodin®, a product of E. Bilhuber, Inc.

Tensodin is indicated in angina pectoris and other coronary and peripheral vascular conditions for its antispasmodic, vasodilator and sedative effects. The usual dose is one or two tablets every four hours.
No narcotic prescription is required.

Each Tensodin tablet contains ethaverine hydrochloride (non-narcotic ethyl homolog of papaverine) ½ grain, phenobarbital ¼ grain and theophylline calcium salicylate 3 grains.

BILHUBER-KNOLL CORP. *distributor* ORANGE NEW JERSEY

Contains: Vial of DENCO Sugar Test (Galatest) and a vial of Acetone Test, dropper instructions and and color chart.

The new plastic **DENCO® urinalysis kit for diabetics**

Your diabetic patients will welcome this new DENCO Urinalysis Kit, combining both easy-to-use DENCO Sugar Test (Galatest) and DENCO Acetone Test. The Kit is made of sturdy plastic, in a pleasing neutral color, unmarked and so attractive.

Dropper and instructions with color chart are included . . . a complete, convenient and simplified unit that fits easily into the pocket or purse of the diabetic patient.

DENCO Reagents Provide Your Diabetic Patients With These Important Advantages:

Simplicity – A little powder . . . a little urine. No test tubes, no measuring, no boiling. Same technique for both tests.

Accuracy – Distinct color reactions immediately. No false positives.

Economy – There is enough powder in each vial for about 100 tests. Each test costs but a fraction of a cent.

Descriptive literature on request. Dept. B-410

THE DENVER CHEMICAL MFG. CO., INC. • NEW YORK, N. Y. • MONTREAL, P. Q.

You can prevent attacks in angina pectoris

Prolonged protection

While Peritrate has been found effective in reducing the number of attacks in almost 80 per cent of patients,[2] comparison with nitroglycerin disclosed that Peritrate exerted "... a marked modifying influence on the electrocardiographic response to standard exercise ... comparable to [results] obtained with glyceryl trinitrate."[1] Unlike glyceryl trinitrate, this *"improved response could be elicited as long as four to five hours after administration of the drug."*[1]

Simple regimen

Together with significant improvement in the EKG,[1,2] Peritrate prophylaxis will reduce the nitroglycerin need in most angina pectoris patients.[3] A continuing schedule of only 1 or 2 tablets 4 times daily will usually

1. *reduce the number of attacks in almost 80 per cent of patients*[2]
2. *reduce the severity of attacks which cannot be prevented.*

Available in 10 mg. tablets in bottles of 100, 500 and 5000.

1. Russek, H. I.; Urbach, K. F.; Doerner, A. A., and Zohman, B. L.: J.A.M.A. *153*:207 (Sept. 19) 1953.
2. Humphreys, P., *et al.*: Angiology *3*:1 (Feb.) 1952.
3. Plotz, M.: New York State J. Med. *52*:2012 (Aug. 15) 1952.

Peritrate®

TETRANITRATE

(BRAND OF PENTAERYTHRITOL TETRANITRATE)

WARNER-CHILCOTT

Laboratories NEW YORK

SARATOGA SPA

has available for a therapeutic program in rheumatic disorders (1) carbonated mineral water baths, (2) electric cabinet treatment, (3) diathermy, (4) infra-ray treatments, (5) mineral water packs and fomentations, (6) massage and salt rub and (7) passive and active exercise.

For literature, write

FRANK W. REYNOLDS, M.D., Ph.D., *Medical Director*
610 Saratoga Springs New York

THE STATE OF NEW YORK . . . THE SARATOGA SPA

SEDATION AND EUPHORIA FOR NERVOUS, IRRITABLE PATIENTS

Use **VALERIANETS-DISPERT**

Req. U. S. Pat. Off.

Each Chocolate Coated Tablet Contains Ext. Valerian (highly concentrated) 0.05 Gm. dispergantized finely subdivided for maximum efficiency

TASTELESS, ODORLESS, NON-DEPRESSANT SEDATIVE and EUPHORIC

VALERIANETS-DISPERT are indicated in cases of nervous excitement and exhaustion, anxiety and depressive states, cardiac and gastrointestinal neuroses, menopausal and menstrual molimena, insomnia.

Dose: 1 or 2 tablets t.i.d. — Bottle of 50 and of 100 tablets

At All Prescription Pharmacies

STANDARD PHARMACEUTICAL CO., INC., 253 West 26th St., New York

For Intestinal Dysfunction
NUCARPON®
Each tablet cont: Extract of Rhubarb, Senna, Precip. Sulfur, Peppermint Oil, Fennel Oil in activated charcoal base.

For making Burow's Solution U.S.P. XIV
WET DRESSING Use
PRESTO-BORO®
(Aluminum Sulfate and Calcium Acetate)
POWDER IN ENVELOPES — TABLETS —

For treatment of Swellings, Inflammations, Sprains

For Pulmonary Conditions
TRANSPULMIN®
3% solution Quinine with 2½% Camphor for intramuscular injection.

PLASTIC AND GLASS EYES

MAGER & GOUGELMAN, Inc.

OVER A CENTURY OF SERVICE • 1851-1952

- PRIVATE FITTINGS
- PERSONAL ATTENTION
- EXPERIENCE & SKILL

510 MADISON AVE., N. Y. 22
Telephone PLaza 5-3756

For twenty years . . .
we have constantly endeavored to serve
the medical profession with . . .

better products for better birth control

Cooper Creme

no finer name in contraceptives

active ingredients:
Trioxymethylene .04%
Sodium Oleate 0.67%

Whittaker Laboratories, Inc.
Peekskill, New York

FREE

Please send: Full Size $1.50 Combination Package Free—Cooper Creme/Dosimeter.

Name _____ M.D.
Address _____
City _____ Zone _____ State _____
2

For the infections common to the fall of the year to which we all are heir, a prescription of choice among physicians the world over is often

Terramycin®

BRAND OF OXYTETRACYCLINE

Worldwide experience over many years has established this well-tolerated, promptly effective, broad-spectrum antibiotic as an agent of choice in the treatment of infections due to susceptible gram-positive and gram-negative bacteria, rickettsiae, spirochetes, certain large viruses and protozoa.

Supplied in convenient dosage forms required for individualized regimens: Terramycin Capsules, Tablets *(sugar coated)*, Pediatric Drops, Oral Suspension, Intravenous, Intramuscular, Ophthalmic *(for solution)*, Ophthalmic Ointment, Ointment *(topical)*, Vaginal Tablets, Troches, Otic, Nasal, Aerosol, Soluble Tablets and Topical Powder.

Pfizer

PFIZER LABORATORIES, Brooklyn 6, N.Y.
Division, Chas. Pfizer & Co., Inc.

IN TENSION AND HYPERTENSION

sedation without hypnosis

℞ Serpasil® T. M.

(reserpine CIBA)

A pure crystalline alkaloid of rauwolfia root first identified, purified and introduced by CIBA

In anxiety, tension, nervousness and mild to severe neuroses—**as well as in hypertension**—SERPASIL provides a nonsoporific tranquilizing effect and a sense of well-being. Tablets, 0.25 mg. (scored) and 0.1 mg.

CIBA

SUMMIT, N. J.

24-hour control

for the majority of diabetics

GLOBIN INSULIN

'B.W. & CO.'®

a clear solution . . . easy to measure accurately

Discovered by Reiner, Searle, and Lang
in The Wellcome Research Laboratories

BURROUGHS WELLCOME & CO. (U.S.A.) INC. • Tuckahoe 7, New York

Out in front...

in treatment

of

hypertension

Raudixin

SQUIBB RAUWOLFIA

More physicians write prescriptions for Raudixin than for all other forms of rauwolfia combined. The reasons for this choice are sound:

- Raudixin contains the standardized whole root of Rauwolfia serpentina. There is no definite evidence that any alkaloid or fraction has all the beneficial actions of the whole crude root.
- Raudixin lowers blood pressure moderately, gradually, safely. It also slows the pulse and has a mild sedative effect.
- Raudixin is the safe hypotensive agent. It causes no dangerous reactions and almost no unpleasant ones.
- Raudixin is often effective alone in mild to moderate hypertension of the labile type. In more severe cases it is effectively combined with other hypotensive agents.

[illegible] and 100 mg. tablets, bottles of 100

Squibb

HOEBER-HARPER BOOKS

3 Major Reference Works

★ HOMBURGER & FISHMAN'S THE PHYSIOPATHOLOGY of CANCER

New Treatise! Filling the need for a cross-discipline survey of current cancer knowledge, this new book by 28 authorities will serve both as a text for courses in Oncology and as a reference tool for investigators. Organized in four parts—Biology; Chemistry and Physics; Clinical Investigation and Practical Applications of the new basic knowledge—it covers a broad range of subjects from experimental cancer to a survey of chemotherapy. Each chapter offers a critical evaluation of information in its field so that the book is not merely a catalog of findings but a sound analysis of progress. To see how valuable this reference is, send for your *On Approval* copy today!

By FREDDY HOMBURGER, M.D., *Research Prof. of Medicine* & WILLIAM H. FISHMAN, Ph.D., *Research Prof. of Biochemistry, Tufts College Medical School.* 1080 pp., 210 illus., $18.00.

★ PASCHKIS, RAKOFF & CANTAROW'S CLINICAL ENDOCRINOLOGY

Outstanding! Here is the first complete and integrated account of the endocrine system, its disorders and its relation to the rest of the body. Based on understanding endocrinopathies as problems in pathologic physiology, it gives you a rational guide to diagnosis and treatment in your own practice. All today's treatments are critically evaluated with recommendations based on the authors' extensive clinical experience.

By KARL E. PASCHKIS, M.D., *Assoc. Prof. of Medicine,* ABRAHAM E. RAKOFF, M.D., *Clin. Prof. of Gynecologic Endocrinology* & ABRAHAM CANTAROW, M.D., *Prof. of Biochemistry, all of Jefferson Medical College.* 611 pp., 253 illus., 5 in full color, $16.00.

★ ADAMS, DENNY-BROWN & PEARSON'S DISEASES of MUSCLE

Unique Monograph! This is the first monograph on muscle diseases to appear in English and the first in any language for several decades. In preparing this systematic account, the authors have not only reviewed the literature but also incorporated their own unpublished findings from extensive research. Several hundred superb microphotographs illuminate the descriptions.

By RAYMOND D. ADAMS, M.D., *Assoc. Clin. Prof. of Neurology, Harvard Med. Sch.,* D. DENNY-BROWN, M.D., *James Jackson Putnam Prof. of Neurology, Harvard Med. Sch.* & CARD M. PEARSON, M.D., *Formerly Mallory Inst. of Pathology, Boston City Hosp.* 371 pp., 330 illus., $16.00.

All Hoeber-Harper Books Sent on Approval

PAUL B. HOEBER, INC.

MEDICAL BOOK DEPARTMENT OF HARPER & BROTHERS

49 East 33rd Street, New York 16, N. Y.